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Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.

Thorner's Psychiatry in General Practice

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By Melvin W. Thorner, M.D., Assistant Professor of Neurology, University of Pennsylvania Graduate School of Medicine. 659 pages, 6" x 9". $8.00.

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EARLY NEUROSYPHILIS

ISRAEL KOPP, M.D.*

BOSTON

INVASION of the central nervous system occurs in nearly all patients during the early stages of syphilis, usually during the first year of the infection. Early neurosyphilis is essentially a leptomeningitis. It is most often asymptomatic. The knowledge of its presence is of great importance since more intensive therapy and careful observation are necessary for these patients.

Early asymptomatic neurosyphilis can be detected only by spinal-fluid examination. The percentage of abnormal spinal fluids depends upon the time and frequency of the examination, ranging from 9 per cent in primary syphilis to 16 and 48 per cent in early and late secondary syphilis.[1] The degree of spinal-fluid abnormality is also of importance, since Moore[2] has shown that with inadequate treatment parenchymatous neurosyphilis will develop in 70 to 80 per cent of patients in whom early examination revealed severe or so-called Group III changes.

Despite these facts, syphilis of the central nervous system has been looked upon by some as a late development of the disease. This attitude has been fostered by the failure to do spinal-fluid examinations in early syphilis, by the rather infrequent appearance of early symptomatic neurosyphilis (meningitis and thromboses) and by the late development of symptomatic parenchymatous neurosyphilis (tabes, paresis, optic atrophy and so forth).

The finding of a normal spinal fluid in early syphilis, of less than two years' duration, does not always indicate that neurosyphilis will not occur in the future. Neurosyphilis may develop despite what is commonly accepted as intensive and adequate therapy with mapharsen, bismuth or penicillin. For this reason it is essential that spinal-fluid examinations be repeated over a period of years before the patient can be given complete assurance that neurosyphilis will not develop. A normal spinal fluid four or five years after the primary lesion, whether therapy has been given or not, will, in nearly all cases, assure the patient against the possibility of future parenchymatous neurosyphilis.

The following case reports bring out some important facts regarding the development, treatment and course of early neurosyphilis.

TABLE 1. *Spinal-Fluid Findings in Case 1.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
1/10/44	Negative	5	Negative	—	Negative	Before treatment
3/ 2/44	+ (0.5 cc.)	—	Negative	—	Negative	Before treatment
9/16/44	Negative	0	Negative	25		After mapharsen and bismuth therapy
7/12/45	+ (0.1 cc.)	218 lymphocytes 5 polymorphonuclears	Positive		Negative	Neurorelapse
9/ 8/45	+ (0.1 cc.)	197 lymphocytes	Trace	59	4444321000	—
10/12/45	+ (0.25 cc.)	5 lymphocytes	Negative	28	0023300000	After malaria and penicillin therapy

CASE REPORTS

In the following case of early asymptomatic neurosyphilis with mild spinal-fluid abnormality the spinal fluid became normal after intensive mapharsen and bismuth therapy. A severe neurorelapse occurred ten months later.

Case 1. H. J. A., a 31-year-old man, developed a penile lesion in October, 1943. The blood Kahn reaction was positive on November 27 and December 6. He was given forty intravenous injections of mapharsen (0.060 gm. each) and

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sixteen intramuscular injections of bismuth subsalicylate (0.200 gm. each) from March 10 to September 16, 1944. The results of spinal-fluid examinations are presented in Table 1.

Neurologic examination on August 30, 1945, was negative. The blood Kahn and Wassermann reactions were positive.

The patient was inoculated with tertian malaria on September 12 and was allowed ten paroxysms until October 6, 1945. He was also given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from September 30 to October 16, 1945.

This case provides an excellent example of the importance of repeated spinal-fluid examinations in early syphilis. The spinal fluid three months after the primary lesion and prior to any chemotherapy was completely normal. Two months thereafter and again before therapy, nervous-system involvement had already occurred, as revealed by a positive spinal-fluid Wassermann reaction in 0.5 cc. The spinal fluid was again completely normal immediately after intensive chemotherapy with mapharsen and bismuth, only to relapse and reveal marked abnormalities ten months later. The high cell count — 223 per cubic millimeter, with 98 per cent lymphocytes — is indicative of a fairly severe meningeal reaction. Since the patient was free of symptoms and neurologic examination was negative, the neurorelapse would have been overlooked had not the spinal-fluid examination been repeated. This type of abnormal fluid is of considerable prognostic significance in the development of future parenchymatous neurosyphilis. Intensive therapy, occasionally reinforced by fever, is necessary if such an event is to be prevented. The finding of even slight spinal-fluid abnormalities in early asymptomatic neurosyphilis is of considerable importance and necessitates frequent clinical and spinal-fluid re-evaluations.

The findings after combined penicillin and malaria therapy revealed the usual marked reduction in cell count and protein. Spinal fluid and clinical re-evaluations were recommended at six-month intervals until the spinal fluid becomes normal and then yearly for three years. Additional therapy, preferably penicillin, will be necessary if clinical or spinal-fluid relapse occurs.

In the following case of asymptomatic neurosyphilis with Group III spinal fluid and marked meningeal reaction nine months after seropositive primary syphilis and immediately after completion of an intensive course of mapharsen and bismuth therapy, spinal-fluid improvement followed additional chemotherapy with mapharsen, bismuth and penicillin.

TABLE 2. *Spinal-Fluid Findings in Case 2.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
10/ 5/44	+		Negative	—	Negative	After bismuth and mapharsen therapy
11/28/44	+ (0.1 cc.)	795 lymphocytes 309 polymorphonuclears	Negative	40	0022210000	—
2/26/45	+ (0.1 cc.)	17 lymphocytes 1 polymorphonuclear	Negative	10	0132200000	After additional chemotherapy

CASE 2. H. A. A., a 22-year-old Negro, developed a penile lesion on February 9, 1944. *Treponema pallidum* was not found on three dark-field examinations. The blood Kahn reaction was positive. Forty intravenous injections of mapharsen (0.060 gm. each) and fifteen intramuscular injections of bismuth subsalicylate (0.200 gm. each) were given from March 20 to September 22. The blood Kahn and Wassermann reactions were positive after treatment. The spinal-fluid findings are presented in Table 2.

The patient was given a second course of thirty-one injections of mapharsen (0.060 gm. each) and eight injections of bismuth subsalicylate (0.200 gm. each) from December 4, 1944, to February 28, 1945, and sixty doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from January 27 to February 6, 1945.

TABLE 3. *Spinal-Fluid Findings in Case 3.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
				mg. per 100 cc.		
7/18/45	—	0	Trace	52.5	3222110000	Xanthochromic fluid; questionable Kahn reaction.
8/ 7/45	++++	—	Positive		5543210000	—
9/ 8/45	+ (0.1 cc.)	2 lymphocytes	Trace	78.0	5554432100	—
11/13/45	+ (0.25 cc.)	2 lymphocytes	Negative	43.0	5443210000	After malaria inoculation and penicillin
	? (0.1 cc.)	1 polymorphonuclear				

Central-nervous-system syphilis was detected shortly after intensive mapharsen and bismuth therapy for primary syphilis. The spinal-fluid abnormalities were severe (Group III). The high cell count indicated a marked meningeal reaction, but there were no symptoms of meningitis. Additional mapharsen, bismuth and penicillin therapy

resulted in a marked reduction of the cell count, but the spinal fluid remained abnormal. Though continued chemotherapy with trivalent arsenicals or penicillin often results in a normal spinal fluid in early neurosyphilis, malarial therapy was recommended. Repeated clinical and spinal-fluid evaluations are necessary for this patient, as recommended in Case 1.

In the following asymptomatic neurosyphilis with Group III spinal fluid ten months after seropositive primary syphilis followed treatment with penicillin, mapharsen and bismuth. Combined malaria and penicillin was then administered.

Case 3. F. R., a 32-year-old Negro, developed a penile lesion in September, 1944. The blood Kahn reaction was positive on September 7.

He was given 60 doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from September 11 to September 18. Because healing of the penile lesion was slow, he was also given forty intravenous injections of mapharsen (0.060 gm. each) and 16 intramuscular injections of bismuth subsalicylate (0.200 gm. each) from November, 1944, to July, 1945. The spinal-fluid findings are shown in Table 3.

Neurologic examination on September 1 was normal.

The patient was inoculated with quartan malaria on September 25 and allowed ten paroxysms to November 10. Fever was also induced on four occasions by means of mixed typhoid vaccine intravenously. He was given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from October 28 to November 12.

Intensive chemotherapy, consisting of penicillin, mapharsen, and bismuth for primary seropositive syphilis, did not prevent the development of asymptomatic neurosyphilis with strong spinal-fluid abnormalities. Involvement of the nervous system was first detected ten months after the primary lesion had appeared and immediately after chemotherapy had been completed. Because of the strong abnormalities in the spinal fluid, malarial therapy combined with penicillin was given. This case reveals the importance of a spinal-fluid examination before the patient is discharged from treatment. Frequent clinical and spinal fluid re-evaluations are necessary, as recommended in Case 1.

In the following case there were marked spinal-fluid abnormalities (Group III) six months after penicillin treatment of secondary syphilis. The patient was also treated with combined penicillin and malaria.

Case 4. A. S. P., a 29-year-old man, admitted repeated exposures in February and March, 1945. Lesions of the anus, penis, gums and tongue were noted on May 8. There was some hoarseness, as well as patchy areas of alopecia involving the scalp and eyebrows. Dark-field examinations of scrapings of the perianal lesion on May 8 and 9 revealed *Treponema pallidum*. A serologic test on May 8 revealed 240 Kahn units.

The patient was given sixty doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from May 9 to May 15. The blood titer had fallen to 40 Kahn units on November 3.

The spinal-fluid findings 6 months after the secondary lesions had appeared and penicillin treatment had been instituted are presented in Table 4.

Neurologic examination was negative on November 17. The patient was inoculated with tertian malaria on January 12, 1946, and allowed nine paroxysms to January 31. He was given one hundred and twenty injections of 30,000 units of penicillin intramuscularly at 3-hour intervals from January 17 to February 1. Spinal-fluid examination after therapy was refused.

Table 4. *Spinal-Fluid Findings in Case 4.*

Date	Wassermann Reaction	Cell Count	Globulin	Total Protein	Gold-Sol Curve
		per cu. mm.		*mg. per 100 cc.*	
11/ 5/45	+ (0.1 cc.)	45	++	—	5544332100
11/20/45	+ (0.1 cc.)	156 lymphocytes	Slight trace	57	5554321000

Penicillin therapy for secondary syphilis did not prevent the development of asymptomatic neurosyphilis with a Group III spinal fluid. The persistence of positive serologic tests should cause one to suspect involvement of the central nervous system. The incidence of neurosyphilis following penicillin therapy of early syphilis is estimated as less than 2 per cent. Repeated courses of penicillin with or without mapharsen and bismuth might well have resulted in a normal spinal fluid since this was a case of early asymptomatic neurosyphilis. However, as long-continued therapy and observation were not possible, combined malaria and penicillin therapy were recommended. If it is among this group that the future paresis or tabes is most apt to develop, early malarial therapy should be of great benefit.

In the following case of asymptomatic neurosyphilis with progressively severe abnormalities in the spinal fluid despite intensive chemotherapy for secondary syphilis, a reversal of Group III spinal fluid to normal occurred after penicillin, malaria and typhoid vaccine fever.

Case 5. M. E. H., a 28-year-old Negro, developed a primary lesion in December, 1943. This was followed by a right inguinal adenitis and a maculopapular rash of the face and back. Dark-field examination of the penile lesion was negative. The blood Kahn and Wassermann reactions were positive in December, 1943, and January, 1944. Forty intravenous injections of mapharsen (0.060 gm. each) and fifteen intramuscular injections of bismuth subsalicylate (0.200 gm. each) were given from January 18 to August 31.

The blood Kahn reaction became negative after treatment, remaining so until February, 1945, and then relapsing to positive. The results of the spinal-fluid examinations are shown in Table 5.

The patient was given eighty doses of 50,000 units intramuscularly of penicillin at 3-hour intervals from March 21 to March 31. He was inoculated with quartan malaria on May 24, and allowed eight paroxysms until July 26. Fever was also induced on seven occasions by means of mixed typhoid vaccine intravenously.

One year after a primary lesion and about three months after completion of intensive chemotherapy, the spinal fluid revealed an increase in cells, which was indicative of central-nervous-system involvement. Two months thereafter the spinal-fluid developed in February, 1944. A diagnosis of lymphogranuloma inguinale was made. He was given sulfonamide therapy. The lymph nodes became less tender but remained enlarged for 3 or 4 months. A serologic test was positive in January and February, 1945. The results of spinal-fluid examination are presented in Table 6.

He was given fifteen intravenous injections of mapharsen (0.060 gm. each) and five intramuscular injections of bismuth subsalicylate (0.200 gm. each) from February 26 to April 13. The spinal fluid reverted to normal in 5 months.

Neurologic examination on June 30 was negative, as was a Frei test on July 7. The blood Kahn and Wassermann reactions were positive.

TABLE 5. *Spinal-Fluid Findings in Case 5.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
12/ 4/44	Not determined	32	—	—	Negative	—
2/ 9/45	—	73	+	—	5555421000	Kahn reaction positive
2/18/45	+ (0.25 cc.) ? (0.1 cc.)	23 lymphocytes 9 polymorphonuclears	+	120	5555321000	—
5/ 1/45	? (1.0 cc.)	15 lymphocytes	+	96	5543310000	After penicillin
8/27/45	Negative (1.0 cc.)	5 lymphocytes	Trace	45	1100000000	After malaria inoculation

abnormalities were severe (Group III). The fluid showed some improvement after the administration of penicillin and became practically normal after fever therapy.

It is possible that the spinal fluid would eventually have become normal as a result of penicillin therapy alone. Moore[3] states that the speed and extent of disappearance of all spinal-fluid abnormalities following penicillin depends upon the degree of these abnormalities before treatment and the duration of the syphilitic infection. In a series of 91 patients with asymptomatic neurosyphilis, 48 of less than four years' duration, observed on an average for about nine months, spinal-fluid normality once obtained seemed to be sustained. Serologic relapse like that in Case 5, which should always alert one to the possible presence of early neurosyphilis, demands a spinal-fluid examination.

In the following case of early asymptomatic neurosyphilis with marked spinal-fluid abnormalities, the spinal fluid became normal after a moderate amount of mapharsen and bismuth therapy.

CASE 6. J. L. R., a 24-year-old man, had negative serologic tests in December, 1942. A penile lesion appeared 7 to 10 days after exposure in December, 1943. Dark-field examinations were negative. Left inguinal adenopathy developed in February, 1944. A diagnosis of lymphogranuloma inguinale was made. He was given sulfonamide therapy. The lymph nodes became less tender but remained enlarged for 3 or 4 months. A serologic test was positive in January and February, 1945. The results of spinal-fluid examination are presented in Table 6.

He was given fifteen intravenous injections of mapharsen (0.060 gm. each) and five intramuscular injections of bismuth subsalicylate (0.200 gm. each) from February 26 to April 13. The spinal fluid reverted to normal in 5 months.

Neurologic examination on June 30 was negative, as was a Frei test on July 7. The blood Kahn and Wassermann reactions were positive.

From July 12 to July 19 the patient was given sixty injections of 40,000 units of penicillin intramuscularly at 3-hour intervals.

The neurosyphilis in this case was asymptomatic and evidently early. The penile lesion in December, 1943, was probably a chancre and not lymphogranuloma inguinale, since a Frei test two and a half years later was negative. A moderate amount of mapharsen and bismuth therapy had rapidly reversed a Group III spinal fluid to normal. This is not uncommon in early asymptomatic neurosyphilis. However, repeated spinal-fluid and clinical re-evaluation for four years at least is necessary since relapse is not uncommon with this degree of abnormality.

TABLE 6. *Spinal-Fluid Findings in Case 6.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
2/15/45	++++	108 lymphocytes 12 polymorphonuclears	—	53.5	5554420000	—
2/28/45	++++	102 lymphocytes 11 polymorphonuclears	—	65.5	5554442000	—
7/ 4/45	Negative (1.0 cc.)	4 lymphocytes	Negative	36.0	1110000000	After bismuth and mapharsen

In the following case of early meningovascular neurosyphilis with right cerebral thrombosis spinal-fluid abnormalities persisted after two courses of penicillin; malaria therapy was instituted.

CASE 7. H. J. B., a 27-year-old man, had a negative serologic test on December 15, 1943. On May 23, 1945, a central weakness of the left facial muscles developed, accompanied by a left hemiparesis. The spinal-fluid findings are shown in Table 7.

The Wassermann and Kahn reactions of the blood were positive on June 8. From June 23 to July 3 eighty doses of

50,000 units of penicillin were administered intramuscularly at 3-hour intervals.

On August 8 neurologic examination revealed brisk and equal reflexes and a left Babinski sign. The serologic tests were again positive. The subsequent spinal-fluid findings are presented in Table 7.

The patient was given a second course of penicillin, consisting of one hundred and twenty doses of 30,000 units intramuscularly at 3-hour intervals from September 7 to 22. Since the protein and cell count remained elevated after completion of penicillin therapy, he was inoculated with tertian malaria and allowed eleven paroxysms.

Early symptomatic neurosyphilis is not common. The patient gave no history of primary or secondary syphilis. The first sign of neurosyphilis was weakness of the left side of the face and left side of the body. This was indicative of a vascular lesion, but pure syphilitic arteritis rarely occurs without an associated meningitis or meningoencephalitis. Though syphilis had been suspected as the cause after the finding of 284 cells per cubic millimeter in the spinal fluid, the Wassermann reaction of the spinal fluid and blood had not been determined. Strong spinal-fluid abnormalities and a positive serologic test were found two weeks thereafter. Spinal-fluid abnormalities were still present after two courses of penicillin, and it was considered best to administer malaria therapy. Clinical and spinal-fluid re-evaluations, as in Case 1, were recommended.

In the following case of early meningovascular neurosyphilis with Jacksonian attacks moderately severe spinal-fluid abnormalities rapidly returned to normal after 2,400,000 units of penicillin had been administered.

Case 8. R. E. R., a 27-year-old man, had a negative serologic test in August, 1942. Because of a gonorrheal infection in July, 1945, he was given four doses of 50,000 units of penicillin intramuscularly. He was again given some penicillin therapy, the exact amount not known, in September because of tonsillitis.

On October 3, he experienced a grand mal seizure with involvement of the right side of the face and right upper extremity. On October 5, 8 and 9 similar episodes without loss of consciousness occurred. During this time he complained of left frontal headaches. Central weakness of the right facial muscles and slurring of speech were observed on October 13.

The quantitative titer of the blood on October 13 and 15 was 10 Kahn units. X-ray study of the skull was negative. The spinal-fluid pressure and dynamics were normal. A sugar tolerance test was normal. The spinal-fluid findings are presented in Table 8.

From October 15 to 22 sixty doses of 40,000 units of penicillin were administered intramuscularly at 3-hour intervals.

Table 7. *Spinal-Fluid Findings in Case 7.*

Date	Wassermann Reaction	Cell Count	Globulin	Total Protein	Gold-Sol Curve	Comment
		per cu. mm.		*mg. per 100 cc.*		
5/23/45	—	284	Negative	—	—	—
6/ 8/45	Positive	99 lymphocytes	++++	23	4433200000	—
8/11/45	+ (0.25 cc.)	25 lymphocytes	Trace	108	Negative	After penicillin
9/24/45	+ (0.5 cc.) ? (0.25 cc.)	27 lymphocytes	Negative	85	0011221000	After additional penicillin
11/ 6/45	+ (0.5 cc.) ? (0.1 cc.)	5 lymphocytes	Negative	90	1100000000	After malaria therapy

Neurologic examination on October 30 revealed central weakness of the right facial muscles, and the reflexes of the right upper extremity were more active than those on the left.

The serologic titer on November 2 was 40 Kahn units; the blood Wassermann reaction was positive.

From January 9 to 16, 1946, the patient was given a second course of penicillin consisting of sixty doses of 40,000 units intramuscularly at 3-hour intervals.

The serologic titer was 10 Kahn units and the blood Wassermann reaction was negative on January 17.

Table 8. *Spinal-Fluid Findings in Case 8.*

Date	Wassermann Reaction	Cell Count	Globulin	Total Protein	Gold-Sol Curve	Comment
		per cu. mm.		*mg. per 100 cc.*		
10/13/45	—	63 lymphocytes 1 polymorphonuclear	—	45	—	Kahn test positive
10/27/45	—	22 lymphocytes	—	32	—	After penicillin
12/ 4/45	Negative (1.0 cc.)	3 lympocytes	Negative	40	Negative	Initial spinal-fluid pressure was equivalent to 145 mm. of water; dynamics normal.

A convulsive episode may be the first indication of neurosyphilis, early or late. This is due to a thrombosis of a cortical vessel that occasionally occurs in the leptomeningitis of neurosyphilis. The moderately severe spinal-fluid abnormalities rapidly reverted to normal after 2,400,000 units of penicillin had been administered. The patient will require clinical and spinal-fluid re-evaluations for at least three years. The convulsive episodes disappear in most cases with adequate antisyphilitic therapy. If they recur, anticonvulsants should be given.

In the following case of syphilitic meningitis with cerebral thrombosis in early syphilis the patient suffered a neurorelapse.

CASE 9. W. R. C., a 21-year-old man, developed a penile lesion in December, 1942. He received three intravenous treatments. A serologic test on February 12 and March 26, 1943, was positive. The spinal-fluid findings are presented in Table 9.

He was given thirty-nine injections of mapharsen (0.060 gm. each) and seventeen of bismuth subsalicylate (0.200 gm. each) from May to December.

From December, 1944, on he experienced frontal headaches of 2 or 3 hours' duration. Dizzy spells occurred in May, 1945. Numbness of the right forearm and the fourth and fifth fingers over 1 week's time was present in August. He was aphasic from September 1 to 8. There was also weakness of the right upper extremity and numbness of the ulnar portion of the forearm.

A serologic test on September 7 revealed 40 Kahn units. Physical examination showed dysarthria, loss of the finer movements of the right hand and absent right abdominal reflexes.

The serologic titer on October 18 was 40 Kahn units; the blood Wassermann reaction was positive.

He was inoculated with tertian malaria on November 17 and allowed eleven paroxysms until December 9. He was also given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from November 22 to December 7.

TABLE 9. *Spinal-Fluid Findings in Case 9.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
5/ 8/43	Negative (0.5 cc.)	110	Negative	—	—	—
12/ 6/43	Negative	2	Negative	—	Negative	After bismuth and mapharsen
10/27/45	+ (0.25 cc.) ? (0.1 cc.)	172 lymphocytes	Trace	76	4443331000	—
12/11/45	+ (0.25 cc.) ? (0.1 cc.)	9 lymphocytes	Trace	46	5443210000	After penicillin and malaria

This patient's spinal fluid revealed an increase in cell count five months after the appearance of a primary lesion. The spinal fluid was normal immediately after the completion of seven months of intensive mapharsen and bismuth therapy. One year later, progressively severe symptoms referable to the central nervous system developed. Neurorelapse with spinal-fluid abnormalities, Group III in type, were found twenty-two months after a normal spinal-fluid had been obtained and three years after the primary lesion.

The sequence of events in this patient again emphasizes the fact that one cannot rely on a single normal spinal-fluid specimen in early neurosyphilis, especially an examination performed shortly after the completion of chemotherapy. In addition, the necessity of adequate therapy for syphilitic meningitis has been stressed by various observers, since two thirds of inadequately treated patients have developed parenchymatous and late meningovascular neurosyphilis.[4] Since the patient's syphilis was of three years' duration, malaria therapy was given without hesitation.

DISCUSSION

The cases reported above are examples of early asymptomatic and symptomatic neurosyphilis. Of 154 cases of asymptomatic neurosyphilis from November, 1944, to February, 1946, 25 (15 per cent) were of less than two years' duration when the patients were first seen. Spinal-fluid abnormalities of varying degree were found from the secondary stage of syphilis on. These abnormalities may clear with chemotherapy, mapharsen, bismuth or penicillin, but occasionally relapse occurs despite intensive therapy.

These cases support the advice that treatment for early syphilis cannot be considered satisfactory unless a spinal-fluid examination is done before the patient is discharged. If the spinal fluid is normal, adequate follow-up study requires that it should be normal again at least four years after the primary lesion. If spinal-fluid abnormalities are present during the first two years of the infection, additional chemotherapy (formerly trivalent arsenicals and bismuth, now penicillin) is necessary, since early neurosyphilis will respond most often to chemotherapy alone. If marked improvement or a normal spinal fluid does not result within a year, fever therapy is given. However, if the infection is of more than two years' duration when the patient is first seen and significant spinal-fluid abnormalities are present, fever therapy should be administered immediately, combined now with penicillin. Further experience will be necessary before it can be determined whether penicillin alone will be adequate in these cases, as has been reported by some observers.[5]

The majority of the patients with early asymptomatic neurosyphilis included in this study had already received chemotherapy consisting of trivalent arsenicals and bismuth. A few had received penicillin. In many cases the treatment was considered adequate according to present standards. With the introduction of penicillin, it is now necessary to determine new methods for the treatment of neurosyphilis. It is already apparent that the incidence of neurosyphilis has been reduced considerably as a result of the treatment of early

syphilis with penicillin. Used alone, the drug has proved very effective in the treatment of syphilitic meningitis, asymptomatic and meningovascular neurosyphilis and, in the opinion of some observers, in parenchymatous neurosyphilis.

It is also evident from the cases reported above that malaria therapy was administered quite early for the treatment of neurosyphilis. Undoubtedly the spinal-fluid abnormalities in some cases would have responded to additional chemotherapy alone. Since it is especially among the patients with severe spinal-fluid abnormalities that future parenchymatous neurosyphilis may develop, and since circumstances prevented long-continued chemotherapy and observation in this group, malaria therapy was given early. Clinical and spinal-fluid evaluations of these patients over the years should be of considerable interest in demonstrating the preventive effect of combined malaria and penicillin therapy of early neurosyphilis upon the development of late parenchymatous disorders.

Prior to the introduction of penicillin, Moore[6] had expressed the opinion that fever therapy in asymptomatic neurosyphilis is seldom necessary except in patients with Group III spinal fluids and those of other groups in whom at least eighteen months of other forms of treatment had failed to effect serologic reversal. Malaria was not recommended by him if the infection was recent until the patient had had at least six months' treatment with the arsphenamines and heavy metal given for the treponemicidal effect. The latter was advised because of the great probability of infectious mucocutaneous relapse. It is possible that this objection can now be overcome by the concurrent use of penicillin, with its pronounced treponemicidal effect, and malaria.

Summary

Invasion of the central nervous system in syphilis is early, occurring in nearly all patients, usually within the first year of the infection.

Early neurosyphilis is most often asymptomatic but occasionally is symptomatic. When asymptomatic, it can be detected only by spinal-fluid examination.

Neurosyphilis may develop despite the administration of what is commonly accepted as adequate chemotherapy for early syphilis.

Complete reliance cannot be placed on the finding of a single normal spinal-fluid specimen in early syphilis before or immediately after therapy.

A negative spinal-fluid examination four years or more after the primary lesion, regardless of whether therapy has been given, is good assurance against the future development of meningovascular or parenchymatous neurosyphilis.

The treatment of early syphilis with penicillin has reduced considerably the incidence of early neurosyphilis. Penicillin alone is of great benefit in the therapy of neurosyphilis of the asymptomatic, meningovascular and meningitic types. Further experience is necessary to determine its value as the sole treatment for parenchymatous (general paresis, tabes dorsalis, optic atrophy and so forth) neurosyphilis.

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HOSPITAL AND HEALTH-CENTER FACILITIES IN MASSACHUSETTS

The Massachusetts State Plan for the Administration of Public Law 725 (Hospital Survey and Construction Act)

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THE acute shortage of hospital beds experienced everywhere in the country during the past few years resulted in 1946 in the enactment of Public Law 725 by the Seventy-Ninth Congress. This act, the Hospital Survey and Construction Act, previously known as Senate Bill 191, or the Hill–Burton Bill, was the first and only bill to be endorsed in Congressional hearings by the American Public Health Association, the American Hospital Association and the American Medical Association. The purpose of the Act is to enable communities throughout the nation to construct hospitals and health-center facilities under a federal grants-in-aid program for a period of five years beginning July 1, 1947. Such facilities are to be provided on the basis of need according to plans developed by each state. The federal Government is contributing a third of the cost of constructing and equipping hospitals and health centers, and the remaining two thirds is derived from sources within the state.

Of the $75,000,000 authorized by Congress for hospital construction during the first year of the program, approximately $1,600,000 has been allotted to Massachusetts. The amount of the grant to Massachusetts for the five-year period of the program totals approximately $8,000,000. Since each dollar of federal grants must be matched by two dollars from state or local sources, the total expenditure under this program in Massachusetts amounts to $24,000,000. State, county, municipal and private nonprofit hospitals may be assisted if individual projects are approved by the state operating agency (usually the health department) and the United States Public Health Service, and provided that the project is in accord with the plan[1] formulated by the state agency to meet the needs for additional facilities. The Massachusetts State Plan was approved by the Surgeon General of the United States Public Health Service on December 2, 1947. The state agency in Massachusetts directly responsible for the administration of Public Law 725 is the Department of Public Health. For the administration of this Act, a bureau of hospital survey and construction has been created, and an advisory council to the state agency has been appointed.

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In accordance with the regulations promulgated by the United States Public Health Service regarding Public Law 725, the Commonwealth of Massachusetts has been divided into three types of hospital service areas — namely, base, intermediate and rural.

A base area is defined as one that, irrespective of population, contains a teaching hospital of a medical school, or one that has a total population of at least 100,000 and contains or will contain a general hospital of 200 beds or more providing internships and at least two or more residencies. An intermediate area has at least 25,000 persons and contains or will contain a general hospital of 100 beds or more. A rural area has a population under 25,000.

For the purposes of the Act, the term "hospital" includes public-health centers, general, tuberculosis, mental-disease and chronic-disease hospitals, and related facilities such as laboratories, outpatient departments, nurses' homes and schools and all service facilities operated in connection with such institutions. Federal hospitals and institutions providing primarily domiciliary care are not included in the above definitions.

Bed allowance for general hospitals is based upon the state's population density. In Massachusetts, with more than 12 persons per square mile, the maximum state allowance for general hospital beds is 4.5 per thousand population. Standards for area ratios also depend on population density. In Massachusetts, area ratio standards are as follows: base areas, 4.5 beds per thousand population; intermediate areas, 4 beds per thousand population; and rural areas, 2.5 beds per thousand population.

The differences in the number of beds allowable under the state and area ratios may be totaled and thus constitute a pool of general-hospital beds. Pool beds may be distributed throughout the state at the discretion of the state agency according to the needs of various areas. The number of beds required to provide adequate hospital services for the care of tuberculosis patients amounts to two and a half times the average annual deaths from tuberculosis, for mental patients, 5 beds per thousand population, and for patients with chronic diseases, 2 beds per thousand population. The total number of public-health centers allowed shall not exceed 1 for 30,000 persons.

In the development of the hospital-construction program, consideration must be given to each of the five categories of facilities: general, tuberculosis and mental and chronic-disease hospitals and public-health centers. New hospitals and additions to existing hospitals have priority over replacements, with the exception of hospitals that constitute a public hazard and should be replaced. It is the intent of the law to provide facilities in areas of greatest need. Special attention must be given to projects in rural areas or in communities of low economic resources.

Existing Facilities

In the development of the state plan for the administration of the Act, a survey of existing hospital and health-center facilities in Massachusetts has been completed. There are in the Commonwealth a total of 219 hospitals with a normal bed capacity of 44,044 beds. Of these institutions, 147 are general hospitals with 16,968 beds, and 24 allied special hospitals with 2210 beds (Table 1).

It is noteworthy that of the 147 general hospitals, 92 have 100 beds or less, 44 have 100 to 249 beds, and only 11 have 250 beds or more (Table 2).

There are 20 tuberculosis institutions with a total bed capacity of 3299 (Table 1). Of these, 4 are nongovernmental, nonprofit associations, and the remaining 16 are governmental hospitals. Of the latter, 12 are owned by cities or counties and provide nearly 2000 beds, primarily for the care of the patients with local settlements, and 2 are state institutions having a bed capacity of about 600 beds. In addition, there are 2 state hospitals caring for patients with extrapulmonary tuberculosis and tuberculosis in children. If tuberculosis units in general or board of health hospitals are included, the total number of existing beds for the care of tuberculosis is 3611.

In Massachusetts there are 24 mental hospitals with a normal bed capacity of 21,050 (Table 1). Of these, 12 institutions with a total of 604 beds are nongovernmental, and the remaining 12 with 20,446 beds are state owned.

Existing facilities for the care of patients with long-term illness are entirely inadequate in the Commonwealth as they are everywhere else in the country. There are now only 1100 beds for patients with chronic diseases in Massachusetts hospitals. How this shortage is to be overcome is a matter of debate. In Springfield, one hospital has set aside a complete ward for such patients. Although this ward was set up more than ten years ago, certain patients admitted at the time of its inception are still occupying beds in this institution. The problem is even more acute for certain categories of patients, such as those with terminal cancer. Ordinarily, these patients are not accepted for admission into general hospitals for indefinite or prolonged periods of stay. Nursing homes and convalescent homes are often too inadequately staffed to care for them. In summary, there are practically no facilities for the patient requiring terminal care.

Table 2. *Distribution of General Hospitals by Size.*

Size	Total Number	
	Hospitals	Beds*
Less than 25 beds	23	436
25–49 beds	32	1,113
50–99 beds	37	2,460
100–249 beds	44	7,178
250–499 beds	8	2,597
More than 500 beds	3	3,184
Totals	147	16,968

*The figures referring to number of beds indicate the normal bed capacity — that is, number of beds for which the hospital was built. In many instances because of overcrowding, this figure is smaller than the actual number of beds in use for inpatient care (complement).

Table 1. *Distribution of Hospitals by Type.*

Type	Total Number			
	Hospitals		Beds*	
General	147		16,968	
Maternity	6		379	
Contagious	6		564	
Other special	12		1,267	
Subtotals of general and allied special		171		19,178
Tuberculosis		20		3,299
Nervous and mental		24		21,050
Chronic and convalescent		4		517
Grand totals		219		44,044

*The figures referring to number of beds indicate the normal bed capacity — that is, the number of beds for which the hospital was built. In many instances because of overcrowding, this figure is smaller than the actual number of beds in use for inpatient care (complement).

Although each of the 351 municipalities is required by law to carry out certain governmental functions in the field of public health, as defined by Public Law 725, there are but 11 health centers in the Commonwealth. Of these, 10 are in Boston proper. The other is the public-health center in Ayer, maintained by the Nashoba Health Unit, a union of several towns in the north central section.

Hospital Service Areas

In keeping with requirements of Public Law 725, all cities and towns in Massachusetts, singly or in groups, are designated as the service areas of existing or proposed general hospitals. Accordingly, the Commonwealth was divided into 70 general-hospital service areas. Each of these areas contains at least one general hospital, with the exception of one area (Athol) where a new hospital facility has been proposed. Determination of the service area was based primarily on available data regarding the flow of patients into the hospital. Other factors taken into consideration were location of trading centers and lines of communication. Subsequently, each hospital service area was clas-

sified as base, intermediate or rural (the prerequisites of these area types were described above). Of the 70 hospital service areas in Massachusetts, 4 are base, 43 intermediate, and 23 rural.

In addition, the state plan provides a method whereby each hospital service area will be co-ordinated with all others so that a uniform pattern of hospital care shall be formulated for the entire Commonwealth. Theoretically, the base areas should offer consultation and diagnostic services to the intermediate areas, which, in turn, offer similar service to rural areas. To allow for this exchange of facilities, Massachusetts was divided into 6 regions of which 3 are composed of intermediate and rural areas, and the other 3 contain in addition base areas. The former are the Beverly-Salem, Barnstable and Pittsfield regions, and the latter, the Boston, Worcester and Springfield regions (Fig. 1).

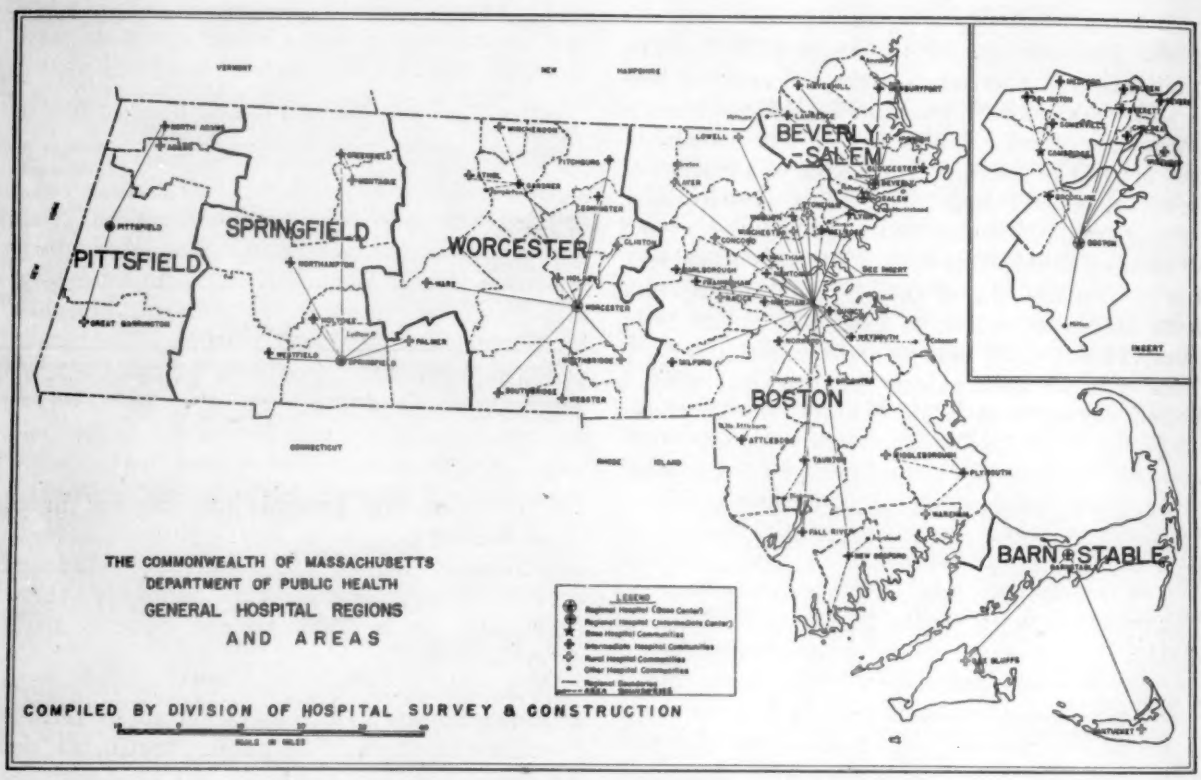

FIGURE 1. *Hospital Service Areas in Massachusetts.*

DETERMINATION OF NEEDS FOR HOSPITALS AND HEALTH CENTERS

The number of beds apportioned to each general hospital service area is determined according to the formula established by law as mentioned above. Of 3944 beds added by area ratio in Massachusetts, nearly all (3285 beds) went to intermediate areas and only 454 and 205 to base and rural areas respectively. Pool beds may be allocated to areas in which the number assigned by area ratio is insufficient for the needs of the jurisdiction. Pool beds were assigned in proportion to high occupancy rates, excessive bed-death ratios and special problems such as seasonal increases in population. Of the 1661 pool beds, the greatest number was allocated to base areas (1011 beds), intermediate areas being allotted 440 and rural areas 210 beds (Table 3).

The number of existing and needed beds according to the several categories is as follows: there are 18,224 general-hospital beds, whereas 23,829 beds are needed according to Public Law 725, making a deficit of 5605 beds. For the care of tuberculosis, Massachusetts has in existence 3604 beds; 4408 beds are needed. Therefore, 804 additional beds must be provided. For patients with mental disease, there are 21,102 beds; 1738 additional beds are needed, since the total beds allowed are 22,840. Finally, for chronic-disease hospital facilities, there are only 1100 beds in existence; 9136 are needed, and therefore, a deficit of 8036 exists. The figures of need met in these four categories of facilities are 76 per cent for general-hospital beds, 82 per cent for tuberculosis, 92 per cent for mental-disease and 12 per cent for chronic-disease beds (Fig. 2).

The state plan must also give consideration to the need for health centers in Massachusetts. For the Commonwealth as a whole, 31 public-health

centers are being proposed. For the most part, these centers have been allocated to the larger cities and towns with a population of 30,000 or more. It should be noted, in accordance with the ratio of 1 health center for each 30,000 persons, that many of the larger cities could plan for more than one health center provided that matching local funds were available. In addition, a health center has been proposed in Amherst for the Connecticut Valley State Health District and another for Barnstable County.

A recent report issued by the Special Commission to Study and Investigate Certain Public Health Matters[2] will suggest a plan to provide full-time health service for the entire Commonwealth. The findings of the Recess Commission will be given full consideration by the state agency and the advisory council in future planning of adequate health-center facilities, including physical plant and personnel.

Priority Schedules

To facilitate the equitable distribution of federal funds available for the construction of general hospitals, a system of priorities has been developed. This system gives full consideration to the provisions required in Public Law 725 and the federal regulations — namely, the relative need for beds in an area, rural character of the hospital service area and the financial rating.

Percentage of need met is determined by division of the total number of existing acceptable beds in each area by the total number of beds needed in the area, this figure being multiplied by 100 for the percentage. Rural character is established by the Act as any area with a population less than 25,000.

In 1941, Dr. Morris B. Lambie[3] conducted a study of the municipal finances of the 351 cities and towns in the Commonwealth at the Harvard Graduate School of Public Administration. His comparative rating of these municipalities was based on three-year averages of three factors: tax rates, assessed per capita valuation, and direct tax per capita. According to these criteria, the municipalities were classified into eleven categories. Communities in the first grouping have relatively greater financial resources than communities low in Dr. Lambie's rating.

The primary consideration in developing the priority schedule was the percentage by which the existing acceptable hospital beds within an area met the total needs of that area. From the percentage of need met, additional deductions were made for rural areas and those of low financial rating. The final figure determined the standing in the priority scheme (Table 4).

Table 3. *Relation of Population to Existing and Proposed General-Hospital Beds.*

Area Type	Existing Beds		Beds Added by Area Ratio	Beds Added from Pool	Total Beds Needed		Population	
	No.	Percentage			No.	Percentage	No.*	Percentage
Base	9,161	50.3	454	1,011	10,626	44.6	1,612	35.3
Intermediate	8,026	44.0	3,285	440	11,751	49.3	2,605	57.0
Rural	1,037	5.7	205	210	1,452	6.1	350	7.7
Totals	18,224		3,944	1,661	23,829		4,567	

*In thousands.

The priority scheme for chronic-hospital projects has been computed in the same manner as for general hospitals, and is based primarily on the percentage of need met. Metropolitan areas of greatest population density will stand highest in the scheme. With respect to general hospitals it became apparent that strict application of the federal formula favored rural and intermediate areas rather than base areas. It was believed that construction of chronic-hospital units in metropolitan areas would compensate in part for the low standing in the priority schedule of the base areas. It will therefore be possible to allocate federal funds for chronic-hospital projects in such areas as Boston, Worcester, Springfield and Pittsfield.

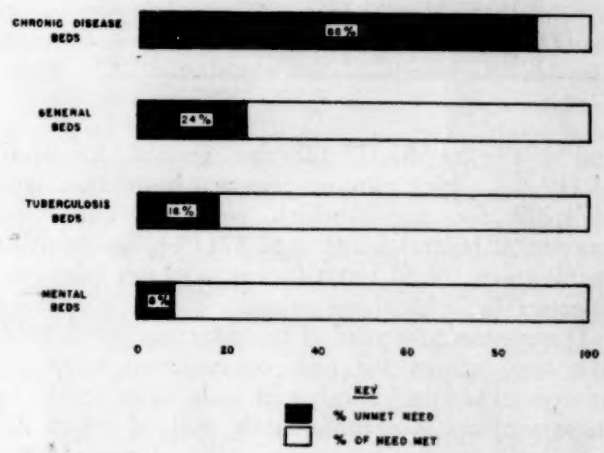

Figure 2. *Need for Additional Hospital Beds in Massachusetts.*

The need for public-health centers in the Commonwealth is so great that no attempt has been made to establish a priority scheme for this cate-

gory. Applications will be considered as they are submitted. It is expected that at least some of the larger communities will take advantage of federal assistance for the construction of health centers.

As indicated above, the need for tuberculosis and mental beds is relatively less than that for beds in chronic and general hospitals. It has been determined that at least for the first two years of the program, federal assistance will be devoted to the construction of general and chronic hospitals and public-health centers.

The federal funds provisionally allotted for these three categories during the fiscal years 1948 and 1949 are $1,177,128 for general hospitals, $1,119,707 for chronic-disease hospitals, and $574,209 for public-health centers. The total amount of federal funds is $2,871,044, representing an allotment of $3,190,050, less a 10 per cent contingency fund for rising prices.

TABLE 4. *Rank of General-Hospital Areas in First Two Priority Groups (1947–1948).*

PRIORITY	AREA NO.	AREA NAME
A-1	R-17	Athol
A-2	I-18	Needham
A-3	I-17	Medford
A-4	R-12	Northbridge
A-5	I-31	Woburn
A-6	I-32	Milford
A-7	R-9	Ipswich
B-1	R-16	Webster
B-2	R-6	Concord
B-3	I-20	Revere
B-4	I-43	Marlboro
B-5	I-21	Somerville
B-6	I-12	Arlington
B-7	I-11	Weymouth
B-8	I-15	Everett
B-9	R-13	Palmer
B-10	I-2	Barnstable
B-11	I-9	Norwood
B-12	I-7	Brockton
B-13	I-5	Plymouth
B-14	I-6	Taunton
B-15	I-28	Melrose

During the first year of the program (1947-1948) five applications for new construction were approved. The total number of beds to be added by these projects is approximately 300, of which 225 are of the general-hospital and 75 of the chronic-hospital category.

DISCUSSION

From Table 3 it is apparent that 50 per cent of existing hospital beds are in base areas that have 35 per cent of the population, whereas 44 per cent of the beds are in intermediate areas with 57 per cent of the population. The figures of the rural areas are more nearly equal — namely, 5.7 per cent of the beds and 7.7 per cent of the population.

After application of the federal formulas developed under Public Law 725, the discrepancies between the percentage of population and the percentage of total beds needed in base and intermediate areas are diminished but not to a marked degree. In other words, the general pattern of the distribution of general-hospital beds in suburban and rural areas has not been altered to a marked extent. It was believed that general hospitals in Massachusetts have grown in accordance with the need of the population for this type of medical facility. It was the policy of the state agency in setting up the plan not to interfere with this natural development.

It is expected that the priority scheme for the general-hospital category will be altered for the second year of the program to take into account obsolescent and substandard facilities. Several of the general hospitals in Massachusetts were built at the turn of the century and are obsolete according to modern specifications. Many are frame buildings or of substandard construction in other respects. It is apparent, therefore, that many beds will be declared noncomputable as far as this plan is concerned. This will alter considerably the priority standing of many areas that are now low in the schedule to a much more favorable position.

Funds allocated by the federal Government for this program are inadequate to fulfill the entire need within the Commonwealth. The state plan indicates an over-all lack of 16,183 beds in all categories. A conservative estimate for the cost of building these beds is roughly $190,000,000, exclusive of public-health centers. It is apparent, therefore, that the total of $24,000,000 that would be spent under this program is by no means adequate to construct all necessary facilities. The cost of construction has risen to such a degree that without federal assistance many projects that have been planned will not be undertaken. All of this may be taken as evidence that Public Law 725 is meeting a great need in the Commonwealth.

SUMMARY

A survey of existing hospital facilities revealed that there are 219 hospitals in Massachusetts with a normal bed capacity of 44,044.

In accordance with the provisions of Public Law 725, the Commonwealth was divided into 70 general hospital service areas of which 4 are base, 43 intermediate and 23 rural. In addition, to provide an integrated hospital system, 6 regions were formed, composed of the service areas mentioned above.

By application of the formulas contained in the Act, it was found that there is a deficit of 16,183 beds, of which 5605 are general, 804 tuberculosis, 1738 mental-disease and 8036 chronic-disease beds.

A priority schedule based primarily upon need for additional beds has been established for general and chronic hospitals.

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PNEUMOCOCCAL PNEUMONIA TREATED WITH AQUEOUS PENICILLIN AT TWELVE-HOUR INTERVALS*

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BALTIMORE

THE efficacy of penicillin in the treatment of patients with pneumococcal lobar pneumonia is well established.[1, 2] However, the manner in which it may be employed to yield the best therapeutic results and with the least discomfort to the patient is still debated. It has been considered that to achieve maximum therapeutic response the blood concentration of penicillin must be maintained constantly at a level greater than the penicillin sensitivity of the particular organism.[3] Because of this assumption penicillin has generally been administered either in aqueous solution at frequent intervals or in some repository form. On the other hand, it has not been demonstrated either experimentally or clinically that this is necessary or desirable.[4] The relation of dosage frequency to therapeutic effectiveness has been examined in a streptococcal infection in mice treated with aqueous penicillin G.[5] The drug was just as effective when given once a day as when given more frequently. Similar results have been reported by others in the treatment of experimental infections in mice.[6–10] A few investigators have successfully employed aqueous penicillin given at infrequent intervals in pneumococcal lobar pneumonia,[1, 11] subacute bacterial endocarditis[12] and pharyngitis due to the beta-hemolytic streptococcus.[13] It seemed worth while, therefore, to extend these observations to the treatment of patients.

PLAN OF STUDY

Pneumococcal lobar pneumonia was chosen for this study because of the relatively sharp clinical end-point obtainable. A consecutive series of patients was treated with aqueous penicillin G given intramuscularly at twelve-hour intervals. The patients were admitted to the public wards of the Johns Hopkins Hospital between October, 1947, and May, 1948. Only cases of clear-cut pneumococcal lobar pneumonia were included, selection being based upon a characteristic history, physical and x-ray evidence of pulmonary consolidation, fever, leukocytosis and the presence of typable pneumococci in the sputum, nasopharynx or blood. There were 82 such cases. All were not seen by us, the care of the patients being primarily the responsibility of the resident staff. An effort was made to retain in the study all patients admitted with pneumococcal lobar pneumonia. However, because of misunderstandings, 3 patients were omitted from the series. They were only moderately ill and recovered uneventfully. Five patients were placed on intermittent intramuscular therapy after a short trial on the twelve-hour schedule. In 2 of these cases the regimen was altered because of the development of complications discussed below. In the remaining 3, discontinuance of the experimental dosage was considered in review to have been arbitrary, and the administration of 100,000 units of penicillin every two hours produced no dramatic alteration of the clinical course. All patients recovered. The total number receiving the trial dosage was therefore 79.

Cultures of the sputum, nasopharynx and blood were obtained before penicillin treatment was started. Most of the patients received a potassium salt of crystalline penicillin G of a single lot number, provided for these studies in 300,000-unit vials. The remainder were given the usual ward supply of penicillin, which varied somewhat as to degree of purity. The penicillin was given intramuscularly in distilled water. The initial dose was 300,000 units repeated at twelve-hour intervals until the temperature had remained normal for forty-eight hours, when 300,000 units was given at twenty-four-hour intervals for an additional forty-eight hours, unless there was some indication for more prolonged therapy. In 2 cases 600,000 units was given initially to severely ill patients.

No control series was established, the number of patients treated at this hospital each year making this impractical. However, there are available for comparison data on the patients with lobar pneumonia treated at this hospital with penicillin during the same period of 1945-1946 and 1946-1947. There were 69 patients in the 1945-1946 series. These were divided almost equally into three groups, receiving respectively 20,000, 40,000 and 80,000 units of aqueous penicillin intramuscularly at three-hour intervals. Fifty-eight patients were treated in 1946-1947 with penicillin in oil and beeswax. The majority of this group were given 300,000 units intramuscularly every twenty-four hours. A few initially received 300,000 units every twelve hours.

Comparative data for the three series regarding population sample, pneumococcal types and severity of disease are shown in Table 1. In general

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the pneumonia was considered to be of average and equal severity in the three groups studied. No deaths or serious complications occurred in the 1945-1946 or 1946-1947 series. However, neither of these groups comprised all the patients admitted because of pneumonia during the years concerned, since a few of the most severely ill patients were given massive amounts of penicillin or a sulfonamide in addition. Death and complications occurred in a few of these excluded patients. Therefore, the mortality and occurrence of complications in these two groups cannot be compared to those of the relatively consecutive 1947-1948 series. But it is valid to use these earlier groups as a basis of comparison of the rapidity of response to penicillin therapy.

Table 1. *Summary of Data.*

Data	Patients Given Aqueous Penicillin (1945–1946)				Patients Given Penicillin in Oil and Beeswax (1946–1947)	Patients Given Aqueous Penicillin (1947–1948)
	20,000 units*	40,000 units*	80,000 units*	total*	300,000 units†	300,000 units‡
Total patients:	23	25	21	69	58	82
Male	14	16	14	44	45	53
Female	9	9	7	25	13	29
Negro	20	19	18	57	52	70
White	3	6	3	12	6	12
Age of patients:						
Under forty years	19	12	13	44	31	52
Forty to fifty-nine years	3	10	7	20	24	27
Sixty years and over	1	3	1	5	3	3
Severity of disease:						
Mild	4	0	1	5	14	14
Moderate	16	16	11	43	37	45
Severe	3	7	4	14	6	19
Critical	0	2	5	7	1	4
Duration of illness:						
Less than two days	7	3	4	14	8	11
Two to three days	11	13	9	33	26	36
Four to six days	5	5	6	16	18	29
Seven days or more	0	4	2	6	6	6
Indications of severity:						
Dehydration	3	4	3	10	18	28
Cyanosis	5	9	3	17	11	9
Jaundice	2	2	4	8	7	7
Disorientation	0	3	3	6	7	11
Shock	0	1	1	2	1	1
Leukopenia (white-cell count below 8000)	1	3	2	6	6	7
Bacteremia	1	5	5	11	8	10
Multilobar	3	8	8	19	12	17
Alcoholism	2	2	2	6	16	18
Cardiac failure	1	1	3	5	2	3
Cardiac disease	2	8	2	12	3	8
Diabetes	0	1	0	1	2	2
Hepatic insufficiency	1	1	0	2	1	3
Pregnancy	1	0	0	1	2	1
Pneumococcal types:						
1–8	7	13	9	29	31	45
Higher types	5	9	6	20	19	27
Untyped	4	6	4	14	8	7
None found	2	2	2	6	0	3
Patients receiving sulfonamides prior to admission	1	1	2	4	3	1

*Every three hours.
†Every twenty-four hours.
‡Every twelve hours.

Results

The response of the patients to the several regimens of penicillin is shown in Table 2 and expressed in terms of total febrile days, total days in bed and period of hospitalization. Within the limitations of this type of clinical study there was no superiority in the response of patients receiving frequent dosages of aqueous penicillin or repository penicillin as contrasted with the response of those receiving aqueous penicillin G at twelve-hour intervals. What minor differences there were favored the latter schedule.

Two deaths occurred in the 82 patients treated during 1947-1948. One happened three hours after admission in a patient with severe hyperthyroidism, auricular fibrillation and cardiac failure after a single injection of 900,000 units of aqueous penicillin. The other occurred seven hours after admission in a patient with a severe head injury who was given 100,000 units of aqueous penicillin intramuscularly at three-hour intervals. Two patients in this group developed complications of their infection. Pneumococcal meningitis appeared in one patient sixteen hours after admission. He had a pneumonia due to a pneumococcus Type 2 with bacteremia. The other complication appeared in a fifty-nine-year-old Negro known to have had chronic pulmonary disease for twelve years. He was admitted with pneumonia of the right upper and

middle lobes due to a Type 7 pneumococcus with bacteremia. Thirteen days after admission cavitation was noted in the right middle lobe. There is a reasonable possibility that both these complications had their inception before the institution of therapy. With the appearance of these complications, the patients were given massive doses of penicillin and sulfonamides. Recovery occurred in both cases.

Only a single patient in the 1947-1948 series developed a penicillin reaction. This followed the use of the highly purified penicillin G and consisted of fever and exfoliative dermatitis on the twelfth day of therapy. No severe local reactions occurred. With aqueous "ward-stock" penicillin at three-hour intervals, the systemic reaction rate was 10 per cent, and with penicillin in oil and beeswax it was 19 per cent. An additional 25 per cent of patients had a local reaction to penicillin in oil and beeswax, characterized by pain, redness and edema at the site of injection.

TABLE 2. *Duration of Fever, Bed Care and Hospitalization after Start of Penicillin in Recovered Patients.*

DATA	PATIENTS GIVEN AQUEOUS PENICILLIN (1945-1946)				PATIENTS GIVEN PENICILLIN IN OIL AND BEESWAX (1946-1947)	PATIENTS GIVEN AQUEOUS PENICILLIN (1947-1948)
	20,000 UNITS*	40,000 UNITS*	80,000 UNITS*	TOTAL*	300,000 UNITS†	300,000 UNITS‡
Total cases	—	—	—	69	58	75§
Duration of fever:						
One day or less	8	1	6	15	10	29
Two days	8	5	6	19	6	18
Three days	2	6	3	11	5	8
More than three days	5	13	6	24	37	20
Days in bed:						
Six or less	10	4	7	21	14	27
Seven to twelve	13	13	5	31	33	41
Thirteen or more	0	5	9	17	11	7
Days in hospital:						
Eight or less	6	1	1	8	6	15
Nine to sixteen	16	14	12	42	33	40
Seventeen or more	1	10	8	19	19	20

*Every three hours.

†Every twenty-four hours.

‡Every twelve hours.

§Excludes 2 deaths, 2 complications and 3 patients who did not start on experimental regimen.

DISCUSSION

Penicillin G in aqueous solution given at twelve-hour intervals was found to be a highly effective means of treating pneumococcal lobar pneumonia. Death and complications each occurred in but 2.4 per cent of the 82 cases. In terms of the number of febrile days, the number of days in bed and the period of hospitalization, the administration of penicillin at twelve-hour intervals was at least as effective as the schedules designed to maintain a constant penicillin blood concentration.

A single dose of 300,000 units of aqueous penicillin G given intramuscularly maintains the concentration in the blood above 0.1 unit per cubic centimeter for only five or six hours,[14] so that for about half the time these patients had little if any circulating penicillin. Since therapeutic response was so satisfactory it appears questionable whether a constant blood level of penicillin is necessary in the treatment of pneumococcal pneumonia. The employment of repository forms such as penicillin in oil and beeswax or procaine penicillin, or the administration of aqueous penicillin at short intervals, is unnecessary in the therapy of lobar pneumonia. Whether infrequent dosage of penicillin in aqueous solution will be effective in the treatment of other infections has not been determined. The experimental work suggests that it would be effective. However, only careful clinical observation will demonstrate how universally this method of therapy may be safely applied.

It is quite likely that the amounts of penicillin G employed in this study were in excess of what is needed for adequate therapy of pneumococcal lobar pneumonia. A total dose of 90,000 to 300,000 units of aqueous penicillin will cure some patients with lobar pneumonia.[1] However, there seems to be little justification for determining the minimal effective dosage of penicillin in a disease with a potential mortality of 30 per cent. This position is supported by the infrequency of complications accompanying the use of fairly brisk dosage and by the lack of toxicity of pure penicillin G. It has been shown in streptococcal infections in mice that a large initial dose of penicillin G keeps the mice alive much longer than the same dose split into smaller fractions, even though the dose is too small to save any of the mice ultimately.[5] It seems wise to use similar large initial priming doses of penicillin G in the treatment of pneumococcal pneumonia and other infections. Such priming doses are an essential part of the successful use of the sulfonamides, and it is a curious circumstance that a similar loading device has not been carried over to the penicil-

lin treatment of infections. In the use of slowly absorbed penicillin preparations such as penicillin in oil and beeswax and procaine penicillin or indeed when penicillin in aqueous solution is given in equal fractions at three-hour intervals, the advantage of a priming dose is lost.

Summary and Conclusion

Two hundred and six cases of pneumococcal lobar pneumonia treated with penicillin are reported. In these cases 79 patients were treated with aqueous penicillin G given intramuscularly every twelve hours, 69 received aqueous penicillin intramuscularly every three hours, and 58 were given penicillin in oil and beeswax.

The patients who were treated with 300,000 units of aqueous penicillin G intramuscularly every twelve hours fared as well as those on the usual schedules of administration.

The intramuscular administration of 300,000 units of aqueous penicillin G every twelve hours is the treatment of choice for pneumococcal lobar pneumonia.

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THE USE OF TESTOSTERONE IN THE TREATMENT OF DEPRESSIONS*

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SEX hormones and related substances have been used in the treatment of depressions for a number of years. Although the use of estrogenic substances of various types has yielded disappointing results in deeply depressed women, the injection of testosterone has been known for a decade or more to cause remission in male patients with depressions, provided large doses are used. Danziger and Blank[1] reviewed the earlier clinical literature bearing on this point; a more recent review by Danziger et al.[2] is also available. The rationale for the use of testosterone in the past has been that of replacement therapy in men past middle life. However, the fact that small doses are ineffective should have suggested the inadequacy of this concept.

Recent studies have shown that electroconvulsive therapy gives rise to effects resembling those caused by the action of some steroid hormones.[3–8] The effects of electroshock therapy that resemble those occurring after the injection of steroid hormones consist, briefly, in fall in plasma protein level, decrease in lymphocytes in the peripheral blood and reduction in eosinophil count, increased diuretic response to water and evidence of extracellular retention of water and sodium. The administration of desoxycorticosterone and of progesterone in large doses having failed here to cause remission of mental symptoms, it was decided to use testosterone; all three of the hormones mentioned have the effect of causing salt and water retention, but only the last has an additional marked anabolic action. The present report summarizes experience here to date.

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Material and Methods

Thirty-one patients, ranging in age from thirty-one to seventy-four years, were given testosterone by injection. They included patients with depressed phase of the manic-depressive psychosis, with involutional psychoses with depression, with reactive depressions and, in 1 case, schizophrenia with a strong depressive component. Only 3 were women, 2 of them having involutional psychoses and the third a manic-depressive psychosis in the depressed phase.

Testosterone was given intramuscularly in doses of 50 mg. daily for two or three weeks; in most cases it was given in two doses of 25 mg. each day. In 1 case the material was given for six weeks, discontinued for a month and given again for a month. After discharge some of the patients were given methyl-testosterone orally, 30 mg. per day. Seven of the patients received electroshock therapy at approximately the same time as the injection of the hormone; 7 had had shock therapy previously, and 6 were given it subsequently.

Observations

Clinical Results

Of the 7 patients, all men, given testosterone at approximately the same time as shock therapy, all improved and were discharged.

In the 17 patients who had not had shock therapy before receiving testosterone, the following effects were noted: improved (discharged), 11 (10 men, 1 woman); discontinued, 2 men; and not improved, 4 men.

Of the 4 men not improved by injection of testosterone, 3 subsequently were given electroshock therapy. All 3 improved, 1 after six treatments in the course of a month, 1 after four treatments a week apart, and 1 after thirty-two shocks given over a period of several months.

Seven patients were given testosterone during relapse after improvement with electroconvulsive therapy, with the following results: 3 men given testosterone one month after relapse were improved (discharged); neither of 2 women given testosterone one month after relapse improved; 1 man given testosterone five months after relapse improved (discharged); and 1 man given testosterone twelve months after relapse showed no improvement.

In 2 patients in this group who recovered after getting testosterone, relapse occurred after the hormone had been discontinued. Brief abstracts of these cases are as follows:

Case 1. A 39-year-old man with a reactive depression was first seen in August, 1946. After five treatments of electroshock, given between December 10 and 20, he improved and gained 8 pounds. Later in that month he suffered a relapse. Eight additional electroshock treatments were given from January 1 to 17, 1947, with improvement and another gain of 8 pounds in weight. Another relapse occurred, and the patient was therefore given 25 mg. of testosterone twice a day from February 8 to 21. He improved, gained 6 pounds and was discharged. A third relapse occurred in May.

Case 2. A 54-year-old man with a manic-depressive (depressed) psychosis was seen in May, 1946. After six electroshock treatments in July he was improved, but during that month he relapsed. From January 17 to 31, 1947, seven electroshock treatments were given, with improvement and a gain of 14 pounds in weight. Another relapse occurred in February, and 25 mg. of testosterone was given twice a day from March 4 to 26. The patient improved and gained 15 pounds, but suffered a further relapse during the following month. In May, improvement and a gain of 9 pounds in weight followed fourteen electroshock treatments.

All 3 patients in this group who did not respond to testosterone were subsequently given shock therapy. The 2 women improved after twelve shocks given over a period of five weeks; they soon relapsed, however. Still another course of shock therapy was then given to 1 of these patients, who died during the treatment, with massive hemorrhage of an adrenal gland. The man in this group improved after six shocks and maintained his improvement for two months before relapsing.

Side Reactions

Two patients could not receive the full course of treatment with testosterone because of the development of edema, tachycardia and severe dyspnea; both were known to have had mild congestive failure previously. Digitalis and ammonium chloride did not influence these symptoms, which remained markedly discomforting for approximately a week. Two other patients exhibited mild edema and shortness of breath; they had no evidence of heart disease.

Two patients exhibited gynecomastia during the course of treatment; one was a man of forty-four who many years previously had had a testicle removed for tumor, and the other was a man of sixty-three with no unusual previous findings in history or physical examination.

The women showed heavy overgrowth of facial hair.

Discussion

The earlier work with testosterone[1, 2] involved the use of the hormone as a form of replacement therapy in men with involutional melancholia. Some authors[1, 2] gave as many as six injections, each of 25 mg. of the hormone, each week for more than twelve weeks. In the present study the rationale of treatment was different in that the hormone was used as a substance with marked anabolic effects and not as a specific sex hormone.

The effect of testosterone is largely or entirely on the affective disorder; paranoid or other serious disturbances in thinking were not changed, and neurotic manifestations were influenced but little. The disappearance of depression, confusion and retardation, however, was definite.

Analysis of the clinical results is difficult. The 7 patients who received electroconvulsive therapy at approximately the same time as the injections of testosterone afford no data for judging the value of the latter. These patients were given testosterone when the course of shock therapy was interrupted by fractures or because the clinical staff believed that the patients' histories raised the possibility of early relapse after shock. In the 11 patients in whom improvement occurred when they were given testosterone not in relation to shock therapy, it is likewise difficult to evaluate the role of the hormone.

The natural history of depressions includes high rates of remission irrespective of therapy; the patients treated here were all receiving psychotherapy during the period of administration of testosterone, and all but 1 were hospitalized. Accordingly, the role of testosterone in relation to clinical improvement cannot be stated with certainty in spite of the fact that individual patients appeared to show no evidence of improvement until after the drug was started. The failures in this group are, however, of interest. They include 2 patients who could not receive the full course of therapy because of aggravation of the manifestations of congestive failure; 4 others who received the full course of injections did not respond, and 3 were then given shock therapy. One improved after thirty-two shocks given over a period of several months, and the other 2 improved after short courses of shock therapy. The last 2 of these patients must be regarded as definite cases of failure of testosterone therapy, but the first patient who received testosterone for only two weeks and then shock therapy for several months need not be.

The results in the patients who received testosterone after relapse following improvement due to electroshock therapy show that the effects of testosterone and of electroshock are interchangeable, at least in some cases. The only failure in the men was a patient who received testosterone a year after receiving shock therapy; he subsequently improved again with shock therapy. Possibly a longer course of testosterone should have been given in his case if one can judge by the results in the man who was given testosterone five months after shock; this patient required six weeks of testosterone for striking benefit to be obtained, although he showed some improvement after two weeks. The 2 women who failed to respond to testosterone given a month after relapse following improvement with shock therapy received the drug for three weeks; both required five weeks of shock therapy for temporary remission of their depressions.

It is possible, judging from the earlier work cited above,[1, 2] that longer courses of treatment with testosterone would have helped some of the patients who showed no improvement in the present study. Long courses have not been employed here as a rule because of the untoward cosmetic effects in women, and because of the more rapid improvement caused by electroshock therapy in patients who might be suicidal; the expense of unnecessary prolongation of hospitalization was also taken into account.

The untoward effects of testosterone therapy — that is, hirsutism in women and excessive salt retention in patients with myocardial insufficiency — were expected. The occasional occurrence of gynecomastia resembles that reported by McCullagh and Rossmiller[9] in patients receiving androgen therapy.

The fact that the effects of testosterone and of electroshock therapy are interchangeable supports the concept that the physiologic changes indicative of increased production of some steroid hormones seen during shock therapy are causally related to remission of mental disease caused by the latter. Since the steroid hormone effects involved are not those of salt and water retention but seem to be an anabolic reaction, it is possible that the effects of electroshock therapy are primarily reparative and, if at all destructive, ony incidentally so. This concept may explain the fact that affective disorders occurring during the course of such destructive processes as general paresis and multiple sclerosis are benefited by shock therapy.

Summary and Conclusions

The administration of testosterone in large doses is followed by remission of mental symptoms in some patients with all types of depression. The hormone acts apparently not as a specific sex hormone but as a substance with strong anabolic effects. In some patients it can be shown that the effects of electroshock and of testosterone are interchangeable, a phenomenon that suggests that the beneficial effects of convulsant therapy are the results of increased production of some steroid hormones. It is not unlikely that the favorable effects of electroshock therapy are reparative and not destructive.

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POLLEN SENSITIVITY IN 100 ASTHMATIC CHILDREN

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IT IS well known that pollen sensitivity is common in asthmatic children. The full importance of this, however, is not generally appreciated, and in most textbooks and other discussions of asthma in childhood more emphasis is given to such allergens as house dust, animal danders and foods than to pollens. In my experience pollen sensitization and the common infectious cold are the two most frequent causes of asthmatic attacks in children, and the number of cases that are helped by removal of a cat, a mattress or some food is small indeed when compared with those in which the attacks are precipitated by pollen or infectious colds.

In an allergy practice or clinic devoted to adults, patients with uncomplicated hay fever predominate. With children this is not so, and of 100 consecutive cases of respiratory allergy from my office files there were 80 cases of asthma and only 20 of hay fever. A high proportion of children who begin with hay fever have pollen asthma after a few seasons.

The pollen season in New England lasts about six months (from April 15 to October 10), and in children the majority of attacks of asthma occurring during this period are due to pollen.

Of 100 asthmatic patients between the ages of three and twelve years tabulated in alphabetic order from my office records, 70 gave positive scratch tests to one or more pollens. In contrast to positive tests with foods (about 20 per cent etiologic), a positive test with pollen as a rule indicates clinical sensitivity. Among the 70 children who gave positive reactions to pollen there were 225† positive tests. Of these, approximately 90 per cent were thought to be of clinical significance (Table 1).

INTRACUTANEOUS TESTS

As a rule, skin sensitivity to pollen in children is not of such high degree as that in adults. The younger the child and the shorter time he has had symptoms the more likely is this to be so. The more delicate intracutaneous test often reveals sensitization when the scratch test will not. It is my practice first to do scratch tests with pollens as a routine on all asthmatic patients, which are followed by intracutaneous tests if the child has symptoms during the season of any pollen and fails to react to it by scratch test. In children the scratch test can by no means be relied upon to demonstrate pollen sensitization.

Intracutaneous tests were done on 20 of the 30 children who failed to give a positive scratch test to any pollen. There were positive reactions to one or more pollens in 14. Of the 100 children under discussion, therefore, 84 gave positive tests, either scratch or intracutaneous, to pollen. All the positive intracutaneous tests were presumably of clinical significance, since they were done only on a selected group, whose histories suggested clinical sensitivity.

TABLE 1. *Positive Scratch Tests to Pollens in 100 Asthmatic Children.*

POLLEN	NO. OF POSITIVE TESTS
Birch	26
Maple	18
Ash	3
Elm	5
Oak	10
English plantain	4
Grass pollen	40
Ragweed	45

TREE POLLEN

In New England birch and oak are the most important trees as far as asthma is concerned. Maple pollen gives a good many positive reactions, but is relatively unimportant as a cause of asthma, for it is heavy and sticky and is therefore not disseminated as readily as birch and oak pollen.

GRASS POLLEN

Twenty-two patients reacted to all the four grass pollens employed in scratch tests; 18 reacted to one or more, but not to all. There were 28 patients who gave positive intracutaneous but negative scratch tests to grass pollen. There were therefore 68 out of 100 who reacted to grass pollen. Positive scratch tests were about equally divided between the four grasses, as follows: timothy, 30; red top, 27; June grass, 28; and orchard grass 29.

RAGWEED

In 28 patients there was a positive intracutaneous test to ragweed with a negative scratch test. There were therefore 73 out of the 100 children who reacted to this pollen.

ASSOCIATED SENSITIZATIONS

There was no child who reacted to pollen who did not also react to other environmental allergens. House dust, cat hair and mold (alternaria or hormodendrum) were the most common, with 65 positive reactions to dust, 39 to cat hair, and 38 to

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†The discrepancy between this figure and the sum total of the figures given in the table is because tests were done with four different grass pollens, and usually more than one gave positive tests.

mold. I doubt whether uncomplicated pollen allergy exists in asthmatic children, and it is uncommon in children with hay fever. This is a very different situation from that in adults, among whom uncomplicated pollen allergy in hay fever is common.

Summary and Conclusions

In a series of 100 asthmatic children between the ages of three and twelve years, there were positive skin reactions to one or more pollens in 84.

Approximately 90 per cent of these reactions were of clinical significance.

The scratch test, particularly in children, is frequently not delicate enough to demonstrate pollen sensitization.

Asthmatic children who are sensitized to pollen are always sensitized to other environmental allergens as well.

The importance of pollen sensitization in the asthma of children is not sufficiently appreciated. In New England, pollen is the most important factor contributing to asthma in children during the spring, summer and early fall — approximately six months of the year.

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MEDICAL PROGRESS

BAL (Concluded)*

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BOSTON

Arsenic

Stocken and Thompson[39] found that the topical application of BAL to lewisite burns was followed by an increase in the urinary excretion of arsenic. These authors then demonstrated that parenteral administration of BAL saved rats poisoned by the application of lethal amounts of lewisite to the body surface. Harrison and his co-workers[40] concluded from their experiments on dogs that the most effective way to treat extensive lewisite burns was to use BAL ointment to combat the local skin effects of lewisite, and, at the same time, to use the compound parenterally to combat the effects of the absorbed arsenic.

Eagle et al.[4] have shown that BAL applied to the skin or given parenterally was effective in the treatment of acute and subacute arsenic poisoning in various animals. In animals so treated, there was a striking increase in the rate of urinary arsenic excretion with the peak of excretion coming two to four hours after the administration of BAL. In conjunction with these findings, Riker and Rosenfield,[41] in studies on the effect of BAL on mapharsen-poisoned cats, found that it increased the concentration of arsenic in the plasma. After the injection of BAL, a high level of plasma arsenic was reached within one hour and a peak at two hours. These results were considered to be in accord with the concept that BAL effects a withdrawal of arsenic from the tissues.

Peters and Stocken[42] prepared a complex from mapharsen and BAL and found it to be more toxic than either BAL or arsenic alone. However, when this complex was injected together with one mole excess of BAL, it was only one fifth as toxic as arsenic alone. The authors suggested that this phenomenon could be explained by the dissociation of the mapharsen-BAL complex to release arsenic in areas where it could cause the maximum toxic effects. However, when excess BAL was present, the extent of dissociation and, consequently, the toxicity of the complex were decreased. Another explanation may be that one mole of arsenic can unite with one or two moles of BAL to form complexes of greatly different properties, as cadmium and mercury do.[43, 44] Even more paradoxical are the findings of Koppanyi and Sperling,[45] who gave BAL to rabbits that had received nonlethal doses of sodium *arsenite*, and found that the animals developed intense central-nervous-system stimulation. The same amounts of arsenite or BAL alone did not produce symptoms, and massive doses of a preformed arsenite-BAL complex were likewise nontoxic. Similar effects were not noted with arsenates or organic arsenicals. On the basis of these experiments, the authors warned that persons poisoned by arsenites (such as Fowler's solution) might conceivably develop undesirable side effects if treated with BAL.

Several investigators have studied the effect of BAL and related compounds on arsine poisoning. Inhalation of this extremely toxic gas may cause intense hemolysis of the red blood cells, with subsequent hemoglobin nephrosis. It is also an inhibitor of tissue respiration. Kensler et al.[46] found that

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BAL was ineffective in preventing in vitro hemolysis of red blood cells by arsine, whereas a related compound, BAL ethyl ether (2, 3-dimercaptopropylether), worked very well. These findings were borne out in arsine inhalation poisoning in rabbits and cats, in which BAL ethyl ether given immediately after exposure was found to be an effective agent, whereas BAL was useless.[46, 47] Because of its great toxicity, it seems unlikely that BAL ethyl ether will be of value in the treatment of arsine poisoning among human beings. Levvy[48] found that another compound, ethane-1:2-dithiol, given intraperitoneally decreased the toxicity of arsine for mice. This compound was effective when given as long as three to four hours after exposure to arsine.

Hughes,[49] studying the effects of lewisite on the rabbit eye, found that it produced rapid necrosis of the cornea and conjunctiva, and that arsenic liberated from the lewisite rapidly penetrated into the chambers of the eye. BAL, in a 5 per cent ointment, proved to be a satisfactory antidote because it not only detoxified the lewisite at the surface of the eye but also rapidly penetrated the tissues of the eye to unite with the arsenic there. Because of the rapid action of lewisite, the ointment had to be applied within two minutes of the lewisite to protect the eye completely; if applied after thirty minutes, permanent damage from the lewisite always occurred. BAL itself in ointment concentrations greater than 5 per cent was found to produce a transient opacification of the superficial layers of the cornea.

Clinical Uses

After it became apparent that BAL was effective against arsenic poisoning in animals, it was tried in various clinics in the treatment of accidental arsenic poisoning and the undesirable side effects occurring in arsenotherapy.

BAL has been used extensively in the treatment of arsenical dermatitis with good results.[30, 50, 51] In severe cases, edema, fever and pruritus disappear or greatly decrease in twenty-four hours, and complete recovery may occur within two weeks. However, some patients respond only partially, or may relapse and require another course of BAL, whereas others may show no improvement at all. Occasionally, as has been noted, abscesses, which are probably due to secondary infection, occur at the sites of intramuscular injection. Although inunctions of BAL are beneficial in dermatitis, they are not so effective as intramuscular injections and may cause skin sensitization to BAL.

Eagle and Magnuson[30] have reported the results of BAL therapy in 55 cases of arsenical encephalitis, usually a lethal complication of arsenotherapy. Only 11 patients died, and in 5 of these BAL therapy was not started until nine to seventy-two hours after the onset of encephalitis. These workers likewise studied the value of BAL in the treatment of 16 patients with so-called post-arsenical jaundice. Only 5 of the 16 patients recovered within ten days of initiation of therapy. The results in this small series of cases suggest that BAL is not very effective in postarsenical hepatitis, but it must be remembered that some authorities consider this condition to be an infection rather than a toxic manifestation of arsenic.

BAL has been of value in some blood dyscrasias associated with arsenotherapy. Eagle and Magnuson[30] reported the failure of BAL to affect the course of 3 cases of aplastic anemia and 1 case of agranulocytosis with thrombocytopenia occurring in persons undergoing arsenotherapy. On the other hand, 10 cases of agranulocytosis responded promptly to BAL — all showing an increase in granulocytes by the second day and a normal count by the seventh day. Holley[52] reported equally good results in 12 cases of arsenical agranulocytosis treated with BAL. Schrumpf[53] reported a favorable result following BAL in a patient with thrombocytopenic hemorrhages associated with neoarsphenamine therapy. In 11 days there was an increase in the platelet count from 2500 to 280,000.

BAL has been used in 4 patients who had received massive doses of mapharsen by error.[30] Three patients had received doses of between 400 and 600 mg. of mapharsen each and made uneventful recoveries after the administration of BAL. The fourth patient was given 1200 mg. of mapharsen and died after inadequate BAL treatment in spite of an initially favorable response.

Several cases of optic complications following arsenotherapy have been treated by BAL. Eagle and Magnuson[30] reported a good response in 3 of 6 patients with visual impairment associated with tryparsamide therapy. Friedenberg[54] observed that a tabetic patient in whom a decrease in visual fields followed tryparsamide therapy had a return of vision after the administration of BAL.

Woody and Kometani[32] have reported on the use of BAL in a large group of infants and children. They treated 42 infants and children who had ingested arsenic-containing substances. Of these, 22 had taken potentially lethal amounts of arsenic. There were no deaths in this series, and in all cases signs and symptoms of arsenic poisoning disappeared within twelve hours of the initiation of BAL therapy.

Mercury

It has been shown that BAL can both prevent the inhibitory effect of mercuric chloride on a brain brei preparation, and reactivate the enzyme succinoxidase after mercury inactivation.[55, 56]

Studies with BAL, BAL glucoside and the monothiol thiosorbitol[44] demonstrated that all three could protect rabbits against acute mercury poisoning if therapy was begun properly. Quantitative evalu-

ation of the protective activity of these compounds showed that the dithiols were far superior to thiosorbitol. BAL glucoside proved to be more active than BAL itself. Rabbits receiving inadequate doses of the thiol compounds died of renal failure. It is interesting to note that although BAL and BAL glucoside can also prevent the development of fatal renal damage in dogs after large intravenous doses of mercuric chloride, some of the animals succumbed to acute pulmonary edema. When mercuric chloride was given orally, BAL and BAL glucoside were also effective in preventing renal deaths, but some of the animals died of a hemorrhagic gastroenteritis.

Because of the extensive use of sodium formaldehyde sulfoxylate as an antidote for mercury poisoning, Stocken[57] compared the effectiveness of this compound with that of BAL. He found that BAL fully protected rats from lethal doses of mercuric chloride, whereas sodium formaldehyde sulfoxylate proved ineffective under similar conditions.

Human Poisoning

Longcope and Luetscher[58] have used BAL extensively in the treatment of acute poisoning in man after the ingestion of mercury bichloride. They reported that of 42 patients suffering from acute mercury poisoning in whom BAL was used, only 2 died. These 2 patients were in a group of 5 cases in which BAL was not started until six to forty-two hours after the ingestion of mercury. Not one of 37 patients receiving BAL within four hours died, regardless of the severity of symptoms or the amount of mercury taken. This stresses the importance of instituting BAL therapy at the earliest possible moment. However, one should not overlook the value of general supportive measures such as intravenous fluids and transfusions. The schedule of BAL treatment for mercury poisoning recommended by the Council on Pharmacy and Chemistry of the American Medical Association (as listed below under dosage schedules) is based on the experience of these authors.

Effects on Mercurial Diuretics

BAL can prevent the occurrence of convulsions and cardiac arrhythmias produced in experimental animals by the administration of mercurial diuretics. It can also prevent the characteristic diuresis produced by these drugs.[59–64] In contrast to BAL, which inhibits both the toxic and the diuretic effects, the monothiols cysteine and glutathione can protect the hearts of animals against toxic effects of the mercurial diuretic mersalyl without abolishing its diuretic effect.[65] Further evidence that monothiols reduce the toxicity of mercurials is supplied by the work of Lehman,[66] who synthesized a diuretic containing thioglycollic acid that proved to be only one-four-hundredth to one-six-hundredth as toxic as comparably effective mercurial diuretics. These findings suggest the possibility of using certain monothiols either in chemical combination or by simultaneous administration to abolish the undesirable effects of mercurials without impairing their diuretic action. However, each mercurial compound must be thoroughly investigated before clinical use in such a manner, because Cohen[67] has reported that a number of alkyl mercuric thioglycollates can produce severe central-nervous-system effects.

Acrodynia

Because mercury has recently been suspected of having a causal relation to acrodynia, Bivings and Lewis[68] gave a twelve-day course of BAL to an infant in whom the diagnosis of acrodynia had been made. It is of interest that this infant had been given twelve doses of calomel and rhubarb a number of weeks before the onset of the signs and symptoms that led to the diagnosis of acrodynia. The urine showed a mercury concentration of 100 microgm. per 100 cc. before the initiation of BAL therapy. Eight days after the last dose of BAL, the urine was found to be free of mercury, and a week or two later all signs and symptoms of acrodynia had disappeared.

GOLD

Thompson and Whittaker[55] found that BAL can protect the brain pyruvate oxidase system from the toxic effects of gold. However, the striking difference in effectiveness between dithiols and monothiols noted in arsenic poisoning was not found: glutathione gave the same degree of protection against gold inhibition as BAL did.

Gold therapy is used extensively in rheumatoid arthritis although it is a potentially toxic agent capable of causing pruritus, dermatitis, stomatitis, agranulocytosis, thrombocytopenia and other disorders. BAL has been used in several clinics to treat these complications of gold therapy. Ragan and Boots[69] reported a series of 5 patients with gold dermatitis who were treated with BAL. In 4 patients there was prompt subsidence of pruritus, and the rash disappeared within one month of BAL treatment. No change took place in the fifth patient's condition. All patients showed an increase in excretion of urinary gold, concurrent with the administration of BAL. Four of the patients had a recurrence of arthritic symptoms shortly after the BAL treatment, offering some support to the contention that chrysotherapy has only a temporary effect on rheumatoid arthritis. Cohen et al.[70] found that BAL caused prompt recovery in 5 cases of gold dermatitis of short duration. The authors attribute these excellent results, in part, to the fact that BAL therapy was instituted early in each case. Margolis and Caplan[71] state that in their experience BAL was of marked benefit in a case of severe stomatitis and a case of dermatitis and sto-

matitis, of possible benefit in 2 cases of dermatitis and of no value in a case of dermatitis of moderately short duration.

Lockie and his co-workers[72] found BAL to be strikingly effective in the treatment of 2 patients with blood dyscrasias following chrysotherapy. A patient with thrombocytopenia, bleeding gums and coma from a possible subarachnoid hemorrhage responded to BAL within several days and had a concurrent increase in platelets from 15,000 to 120,000. The other patient had agranulocytosis, and within seventy-two hours after initiation of BAL therapy the granulocytes increased from zero to 17 per cent, and by the seventh day they had increased to 45 per cent.

Lead

Although BAL can reverse the lead inhibition of the sulfhydryl-containing enzyme, succinoxidase,[56] and can increase the urinary output of lead, there is no satisfactory evidence that it is of value in the treatment of lead poisoning.

Animal Studies

Braun et al.[73] concluded that BAL was ineffective in both acute and chronic experimental lead poisoning. They gave BAL to rabbits poisoned by a single large dose of lead nitrate and to others poisoned by multiple small doses of lead nitrate, and in each case the mortality in animals treated with BAL was greater than that in animals receiving lead nitrate alone. This suggested that BAL had an additive effect. Germuth and Eagle[74] likewise found that BAL failed to protect rabbits against acute or chronic lead poisoning, and in one group of animals found that BAL hastened the onset of death. BAL did cause a marked increase in the urinary excretion of lead, but this response decreased with each subsequent injection. The period of increased urinary excretion of lead began immediately after the injection of BAL, reached a peak in about two hours and then returned to the preinjection level in three or four hours. A preformed lead-BAL complex was injected into rabbits and found to be almost as toxic as lead acetate, despite the fact that it had a low dissociation constant. These authors concluded that BAL can release some lead from its combination with the tissues and force it to be excreted in the urine, but that the amount of lead thus eliminated is too small to effect the eventual outcome of the poisoning. In addition, they pointed out the possibility that a toxic lead-BAL complex could be formed in vivo, and postulated that this could account for the additive effects of BAL in experimental lead poisoning.

Chiodi and Sammartino[75] were able to increase the weight of rat kidneys by the daily administration of lead acetate. This increase in kidney weight did not appear when BAL was given concurrently with the lead acetate.

Human Poisoning

Telfer[76] studied the effect of BAL on a patient suspected of having lead poisoning. Although prior to BAL therapy the patient's urinary output of lead was within normal limits, the urinary lead excretion increased after therapy.

Ryder and his co-workers[77] studied the effects of a single intramuscular dose of BAL on the lead concentration in the blood and urine of men who had been exposed to lead. After BAL the concentration of lead in the whole blood started to fall within seven and a half minutes, reached a minimum in eight hours and returned to the original level in twenty-four hours. Simultaneously, there was an increase in the urinary output of lead. This effect could be produced repeatedly by subsequent injections of BAL. In spite of the reduction in the whole-blood lead concentration by BAL, the plasma levels were unaffected, indicating that large amounts of lead were released from the erythrocytes and rapidly removed from the blood stream. Although BAL produced these findings, which are of interest, it failed to shorten the clinical course of lead intoxication.

Cadmium

Cadmium is a sulfhydryl enzyme inhibitor, and its inhibitory effect can be reversed by BAL and other dithiols. The monothiol glutathione can bring about reactivation also, but only when given in large amounts.[56]

Lethal doses of cadmium given parenterally cause intense gastrointestinal activity, muscular weakness, prostration, severe dyspnea and death within twenty-four hours. Gilman and his co-workers[43] found that BAL could prevent this acute death from taking place in rabbits, if it were given just prior to the cadmium, but a delayed death from renal damage invariably occurred. Paradoxically, when BAL was given thirty minutes after a lethal dose of cadmium, only 50 per cent of the animals died, although, again, all deaths were the result of renal failure. More effective than BAL was BAL glucoside, which protected the majority of animals from the lethal effects of cadmium. Thiosorbitol and thioxylate, both monothiols, saved only a limited number of animals from cadmium deaths. Strangely enough, all the fatal results in the monothiol-treated animals were from typical acute cadmium poisoning rather than from renal damage as in animals dying after BAL and BAL glucoside therapy. The authors postulated that the renal deaths following BAL therapy could be explained by the assumption that BAL and cadmium form a relatively unstable complex. Hence, although BAL diverts the cadmium away from tissues usually affected by this metal, it carries it to the kidney, where enough cadmium dissociates to cause severe renal damage. The decrease in renal damage seen

when BAL is given thirty minutes after the administration of cadmium is explained by the supposition that some of the cadmium becomes irreversibly fixed in the tissues, and thus a smaller amount eventually reaches the kidneys.

The same authors found that, depending upon the pH of the solution, cadmium united with one or two moles of BAL to form two different complexes: Cd-BAL and Cd $(BAL)_2$. Cadmium also formed similar complexes with BAL glucoside, thiosorbitol, and thioxylate. Although the Cd-$(BAL)_2$ complex had a low dissociation constant in vitro, a readily available supply of cadmium ions seemed to be available when this complex was preformed and then injected into rabbits. Depending upon the amount given, the animals died either acutely from typical cadmium poisoning or several days later from renal impairment. Preformed Cd $(BAL\ glucoside)_2$ proved to be relatively nontoxic, probably because the complex is too large to be absorbed readily by the renal cells.

Both BAL and BAL glucoside were found to increase the excretion of cadmium from cadmium-poisoned animals. The BAL-treated animals showed an increase in both urinary and fecal cadmium, whereas those treated with BAL glucoside showed an increase in urinary cadmium only.[78]

In an extensive inhalation study in dogs and mice, it has been shown that cadmium mists can cause acute death from massive pulmonary edema, or delayed death from diffuse pneumonitis often associated with lung abscesses, anorexia, bloody diarrhea and generalized wasting. BAL prevented death in a number of animals when it was given one to three hours after the cadmium exposure. However, when BAL was given prior to the exposure to cadmium, it actually hastened death, presumably by fixing the cadmium in the lungs, where it could do the most damage.[79]

Silver

In a limited study, Olcott and Riker[80] found BAL ineffective against experimental argyria. They gave small daily doses of silver nitrate to 2 white rats for four hundred and fifty-six days. One animal was then given nine injections of BAL over a period of eighteen days. Autopsy and histologic examination showed no essential differences in the amounts of silver deposited in the two animals. The authors concluded that BAL would probably be of no value in the treatment of argyria in man.

Miscellaneous Metals

Antimony

Barron and Kalnitsky[56] reported that attempts to reactivate the succinoxidase enzyme system inhibited by antimony were unsuccessful with BAL, whereas glutathione was effective in reversing this inhibition. On the other hand, Thompson and Whittaker[55] found that BAL not only protected the brain pyruvate oxidase system from inhibition by antimony but also protected rats poisoned with this metal. Eagle and his co-workers[81] observed that BAL protected rabbits poisoned with various antimony compounds. An increase in antimony excretion in the urine persisting for two to four hours occurred after each injection of BAL. Similar results were obtained by Braun et al.[73]

Tellurium

Amdur[82] used BAL to treat 3 men who had inhaled tellurium-containing fumes and developed a characteristic garliclike odor of the breath. Although BAL failed to cause an increased urinary excretion of tellurium, the author believed that it was instrumental in decreasing the duration of halitosis from a possible period of weeks or months to a period of eleven to fourteen days in each case.

Copper, Bismuth, Chromium, Nickel, Zinc, Thallium, Selenium and Vanadium

McDonald[83] has reported that BAL glucoside in small doses caused an increased urinary copper excretion in normal sheep. The excretion reached a maximum of thirty times normal within an hour and then fell rapidly to a normal rate.

In enzyme-inhibition studies, Barron and Kalnitsky[56] found that BAL was effective against zinc, only partly effective against bismuth and totally ineffective against vanadium and selenium. Braun et al.,[73] in animal experiments, found BAL to be an effective antidote in poisoning from bismuth, chromium and nickel, but of no value against thallium and selenium. The administration of BAL actually hastened the death of animals poisoned with the latter metal.

Alloxan

Lazarow[84] reported that large doses of monothiols such as cysteine, glutathione and thioglycollic acid completely protected rats against a diabetogenic dose of alloxan. The dithiol BAL in smaller amounts was found to be equally effective in protecting the animals from alloxan. However, neither the dithiol nor the monothiols protected the animals unless given before or immediately after the administration of alloxan. It has been postulated that alloxan causes an immediate, irreversible change, which can be prevented only by the early use of sulfhydryl groups, and, in contrast to heavy-metal poisonings, this change cannot be reversed by dithiols.

Phenylthiourea

After the introduction of phenylthiourea and ANTU (alpha-naphthyl-thiourea) as powerful rodenticidal agents, a search has been made for suitable antidotes to be used in cases of accidental

poisonings. Harvey and his co-workers,[85] on the basis of the findings of Du Bois[86] that ANTU inhibits sulfhydryl-containing enzymes, investigated the value of BAL and 1-thiosorbitol in phenylthiourea poisoning. ANTU and phenylthiourea are similar in action, and the latter was used in this experiment because of its greater solubility in water. The authors found that 1-thiosorbitol given to rats immediately after the administration of phenylthiourea protected these animals from the toxic and lethal effects of phenylthiourea. On the other hand, BAL increased rather than decreased the toxic effects of phenylthiourea. This paradox of a monothiol affording protection from a substance while a dithiol increases the toxic effects of that substance is similar to a situation seen in cadmium poisoning in which thiosorbitol is effective but BAL fails and even potentiates the action of cadmium.

Dosage Schedules

Sufficient experience in the use of BAL has been accumulated to permit tentative recommendations concerning proper dosage schedules for the treatment of arsenic and mercury poisonings. However, too little clinical information is available, as yet, to justify the formation of specific dosage regimens for the use of BAL in other metal poisonings.

The Council on Pharmacy and Chemistry of the American Medical Association[87] suggests that BAL be given by intramuscular injection according to the following schedules:

For severe arsenic reactions, each injection to contain 3 mg. of BAL per kilogram of body weight.

First day, Second day	6 injections per day, at the rate of one injection every four hours.
Third day	4 injections
Following ten days or until recovery	2 injections per day

For mild arsenic reactions, each injection to contain 2.5 mg. per kilogram.

First day, Second day	4 injections per day
Third day	2 injections
Following ten days or until recovery	one injection per day

For mercury poisoning, larger doses of BAL are suggested. An initial dose of 5 mg. per kilogram of body weight should be given, to be followed in one to two hours by a dose of 2.5 mg. per kilogram. After two to four hours a second dose of 2.5 mg. should be administered, and in severe cases a third dose of 2.5 mg. should be given within the first twelve hours. On the second day, two doses of 2.5 mg. per kilogram should be used, and on the third day one dose of 2.5 mg. per kilogram is to be given.

Woody and Kometani[32] successfully treated 42 infants and children with BAL for arsenic poisoning. Children suspected of arsenic ingestion but without symptoms of arsenic poisoning were given three to six doses of 2.5 mg. per kilogram of body weight each at intervals of four to eight hours. Children with mild symptoms of arsenic poisoning were given six to twelve doses of 2.5 to 3.5 mg. per kilogram each at intervals of four to eight hours. Those with severe symptoms were given six to twelve doses of 3.5 to 5.0 mg. per kilogram each at intervals of four to eight hours.

Summary

BAL (2,3-dimercaptopropanol) was developed as an antidote against poisoning from the arsenic-containing war gas, lewisite. Since it is easily oxidized and unstable in aqueous solutions, BAL is commercially available only in a preparation containing peanut oil and benzyl benzoate, which is suitable for intramuscular administration alone. BAL is of value in the treatment of certain metal poisonings because it displaces the metal from its combination with the sulfhydryl groups of enzyme proteins with the formation of a metal-BAL complex, which is excreted. Although BAL in therapeutic doses may produce unpleasant side effects these are transient. BAL has been shown to be of clinical value in the treatment of arsenic, mercury and gold poisonings. Further clinical studies are necessary before the efficacy of BAL in other metal poisonings can be evaluated. Studies on animals suggest that BAL actually enhances the toxicity of certain metals. Therefore, BAL should not be used indiscriminately in the treatment of metal poisonings.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 34531

PRESENTATION OF CASE

A sixty-one-year-old man was admitted to the hospital because of vomiting and diarrhea of one year's duration.

The diarrhea, which was described as occurring five or six times daily, was watery, brownish and without gross evidence of blood. The vomiting occurred once or twice a week, usually at night after retiring. It was accompanied by moderate epigastric fullness and dull substernal discomfort, which were not apparently related to food ingestion. In the six months before admission frequency of the attacks of vomiting increased to almost every night. At this time the patient noted the onset of burning and rolling sensations in the pit of the stomach. These symptoms were relieved somewhat by the emesis, which was liquid and mucoid in character. Anorexia was very marked. There was no postprandial distress, pain between meals, tarry stools or jaundice. He had lost 70 pounds since the onset of illness.

The past history revealed rheumatoid arthritis since the age of thirty years, when he had a severe attack with involvement of almost every joint. A bilateral knee-joint reconstruction was done after the acute stage. At this time he experienced the onset of mild exertional dyspnea and dependent edema. In spite of this he was alleged to have been in good general health but was unable to work because of the arthritis.

Physical examination revealed an extremely cachectic man in no acute distress. The chest was emphysematous, with limited expansion. There were moist, sibilant rales in the left axilla and at both bases. The heart was not enlarged. The liver edge was palpated four fingerbreadths below the costal margin. The spleen was not felt. A large, reducible, supraumbilical, ventral hernia was present. Marked arthritic changes involving almost every joint, with limitation of movements, were observed. These appeared to be in a quiescent stage.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 5,300,000, with a hemoglobin of 12 gm., and a white-cell count of 21,300, with 70 per cent neutrophils. The urine had a specific gravity of 1.014 and contained no albumin. Subsequent specimens gave +++ to ++++ tests for albumin. There were a few white cells in the sediment. The nonprotein nitrogen was 50 mg., and the total protein 7.75 gm. per 100 cc., with an albumin of 3 gm. and a globulin of 4.75 gm. The chloride was 108 milliequiv. per liter, and the alkaline phosphatase 6.6 units. The prothrombin time was 17 seconds (normal, 16 seconds), the cephalin flocculation test was ++ at twenty-four hours and +++ at forty-eight hours, and the bromsulfalein test showed 10 per cent retention of the dye. A Congo-red test revealed a 52 per cent retention of dye in the serum.

X-ray studies of the gastrointestinal tract gave findings suggestive of pyloric obstruction, with marked pylorospasm. A barium enema was negative. A chest film showed extensive fibrotic emphysematous and bronchiectatic changes in both lungs. An electrocardiographic record was within normal limits. The gastric fluid on analysis revealed high acidity and was guaiac negative. Cytologic study of smears was reported negative. The stools were guaiac negative. After admission repeated gastric aspirations of 150 to 300 cc. resulted in some decrease of the vomiting, but the patient continued complaining of gastric fullness.

On the eighth hospital day a partial gastrectomy and repair of the ventral hernia were performed. Following operation he noted no relief of the gastric fullness and complained of increasing pain and stiffness of joints. The nonprotein nitrogen began to rise, from 50 mg. to 72 to 170 mg., finally reaching 225 mg. per 100 cc., with a fall of the chloride to 78 milliequiv. per liter and of the total protein to 5.4 gm. per 100 cc. The watery diarrhea recurred, and marked dyspnea and cyanosis developed. Moist rales were heard almost to the top of both lungs. On the twenty-second hospital day he became unresponsive and died.

DIFFERENTIAL DIAGNOSIS

DR. BERNARD M. JACOBSON: Can you tell us the figures on the acidity of the gastric fluid?

DR. TRACY B. MALLORY: A fasting specimen was reported as 50 units of free and 80 units of combined acid.

DR. JACOBSON: A considerable degree of acidity.

As I read over this patient's history and before I got to the report of the x-ray examination, a number of thoughts occurred to me about the fundamental diagnosis. Apparently for a considerable period of time there was a watery, brownish diarrhea without gross evidence of blood but with associated cramps in the lower abdomen. The diarrhea seemed more prominent than the vomiting, which occurred only once or twice a week, usually after retiring. The

possibilities that ran through my mind as causes of long-continued diarrhea without pus or blood or tenesmus include a few common conditions and a few unusual conditions that might be mentioned. Against such a condition as ulcerative colitis or regional ileitis was the lack of blood, pus or tenesmus. The presence of a carcinomatous lesion anywhere in the gastrointestinal tract from the stomach downward should certainly be considered. The question of a fistula between various segments of the gastrointestinal tract must be considered, and that could account for this type of diarrhea. The possibilities outside the gastrointestinal tract — general and systemic disease that can cause this type of diarrhea — come to mind. Chronic uremia is one of the commonest. Chronic nitrogen retention can be associated with this type of diarrhea and last many months. One thinks of such diseases as Addison's disease as causing diarrhea and vomiting and also of pernicious anemia and sprue, but the subsequent physical and laboratory findings give no evidence for either Addison's disease, pernicious anemia or sprue, nor is there any evidence later on that suggests hyperthyroidism as the cause of that type of diarrhea. As one goes along a little bit in the history, one finds that when the vomiting became more pronounced, beginning to occur almost daily, the material vomited was liquid and mucoid. I presume we would know from the patient whether the liquid was heavily stained with bile because that is usually mentioned at some time in a patient's history. In the absence of small-bowel content of the vomitus I think we must assume that there was obstruction at the pylorus. This was not low intestinal obstruction. The amount of vomiting, it seems to me, is out of proportion to what we may expect as secondary to some of the systemic diseases I have mentioned.

On physical examination the liver edge was four fingerbreadths below the costal margin. In view of the obvious emphysema I assume the upper border was quite low and the liver was not large but merely ptotic. I am rather surprised we were not told about the examiner's feeling a mass in the abdomen, especially in the presence of the hernia. Perhaps I should not expect to feel a mass, but I think I do.

As far as the laboratory work goes, there are a few items of interest. A mild hypochromic anemia was present. We are told that one urine on admission had a specific gravity of 1.014; probably the patient did not have a specific-gravity concentration test, but it would be of some interest to know if he could concentrate. Most of the urine apparently contained a huge amount of albumin and a few pus cells. I would be interested to know if the patient had an intravenous phenolsulfonephthalein test, since we see later that kidney failure played an important part in the patient's terminal career.

Dr. Mallory: There was a phenolsulfonephthalein excretion of 0 in fifteen minutes, 5 per cent in sixty and 5 per cent in twelve.

Dr. Jacobson: What volume?

Dr. Mallory: No volume was recorded.

Dr. Jacobson: Assuming that the urinary volume was fairly good, this obviously indicates impairment in renal function — no excretion in fifteen minutes.

Dr. Mallory: No concentration test is recorded but subsequent specific gravities are 1.005, 1.003, 1.010 and 1.006.

Dr. Jacobson: Reversal of the albumin-globulin ratio is of some interest, suggesting systemic disease with increasing serum globulin. There is no good evidence of any one disease. Some degenerative disease of the liver might have caused this high serum globulin. Rheumatoid arthritis can sometimes cause high serum globulin. I doubt if that would be suggestive of multiple myeloma or sarcoid or some of the other conditions. I suspect that the globulin may be elevated due to rheumatoid arthritis. The amount of liver-function defect, as measured by the cephalin flocculation and bromsulfalein test, is of no great significance in a person as malnourished as this. Later we note the low serum chloride, which was initially rather high, perhaps because of dehydration. The phosphatase of 6.6 units is against biliary obstruction. The normal prothrombin time is also against marked derangement of liver function.

Dr. Stanley M. Wyman: The films of the chest show a diffuse linear process throughout both lung fields extending from the hili. There are suggestions of dilated bronchi in the periphery of the right-upper-lung field. The hilar shadows are prominent, but I can see no definite lymph nodes or other masses. The heart shadow is not remarkable for a man of this age. The chest is increased in the anteroposterior diameter, and I think the whole picture is quite consistent with fibrosis and emphysema, although of course lymphatic metastases cannot be entirely excluded. The films of one barium-enema examination show an intrinsically normal-appearing colon, with a loop of barium-filled bowel, I think probably ileum, extending out into the hernial sac and other gas-filled loops of bowel, which are probably ileum in the sac. The hepatic flexure is displaced downward, and the upper margin of the liver extends reasonably high, which makes me wonder about increase in the size of the liver from this examination.

The next films are of the gastrointestinal examination done on at least two occasions. I am sure the examiner had a great deal of difficulty with this patient because of the arthritis. I think the important thing on these films is that there is a large, soft-tissue shadow in the right upper quadrant that I believe displaced the duodenum and stomach to the left, and, as one can see in this projection, this lies somewhat anteriorly. Apparently, the examiner had a great deal of difficulty in obtaining good visualization of the pylorus and the distal duodenum, and we have no film with good filling of the distal duodenum. The few traces that we have of barium in the duodenum show a suggestion of some irregularity

in the mucosal pattern. There is a suggestion of some radiolucency overlying the liver. This, again, is not a definite finding. The film that might have shown it best is of unsatisfactory quality. There is one, and only one, spot film that shows an unusual accumulation of barium at this point, which makes one wonder about barium in the common duct. I would say that the liver was enlarged and displaced the stomach. It may be that the second portion of the duodenum is narrowed. I cannot comment intelligently on the pylorus. The changes may be due to extrinsic pressure.

DR. JACOBSON: Dr. Wyman has pointed out that the upper portion of the liver was not low as I suspected and that the stomach was apparently pushed to the left. In that case we must believe the liver was large and was the seat of disease.

The Congo-red test, which showed 52 per cent retention, apparently a doubtful borderline finding, gave no definite evidence of systemic amyloid disease. There are certain forms of amyloid disease — the atypical type that might infiltrate the walls of the small bowel — that will not take up Congo-red dye. We cannot see any visualization of the small bowel — no leakage of barium directly into the colon.

DR. WYMAN: I should not say so.

DR. JACOBSON: If we could have a picture of the upper small bowel, it would be helpful.

DR. WYMAN: This is the closest we came to it. I would consider these jejunal folds to be within normal limits.

DR. JACOBSON: Was an intravenous pyelogram done?

DR. WYMAN: No.

DR. JACOBSON: I rather suspect that the correct diagnosis was not well understood preoperatively and that some of the reasoning that I have gone through was also discussed by the clinicians on the service before operation. This patient obviously had pyloric obstruction. We must assume vomiting secondary to pyloric obstruction and not systemic disease.

What of the diarrhea? We have no evidence of intrinsic small-bowel or large-bowel disease. Can we tie up the vomiting and the diarrhea into one diagnosis? It is possible if we assume that the patient had carcinoma of the pylorus. Many patients with carcinoma of the stomach have diarrhea, the exact mechanism of which we do not know. The evidence for carcinoma of the stomach in this patient is the progressive downhill course. The history of the type of discomfort he had in the stomach is perfectly consistent with it. For the diagnosis of pyloric obstruction due to ulcer there may be more evidence from the laboratory point of view — high gastric acidity and the negative cytologic smear. The lack, however, of a good, clear history of postprandial pain typical of ulcer stands out, and the combination of pyloric obstruction and diarrhea inclines me a little more to the diagnosis of carcinoma rather than ulcer. Some few cases of carcinoma do have high gastric acidity. I cannot visualize any other specific cause for diarrhea.

What happened after operation is certainly an interesting phenomenon. The kidney failure, which may have been very minimal before operation, set in quite promptly. The patient obviously died in uremia. Terminally he had left-sided heart failure and pulmonary edema.

I believe that in recent years major surgery in patients with cardiac disease has become less and less of a risk and that the experience of many surgeons and physicians is that renal failure is probably a most important postoperative condition.

What was the renal failure due to? We have no good evidence that this patient had chronic glomerulonephritis or chronic vascular nephritis, although it may well be that the initial blood pressure of 120 systolic, 80 diastolic, reflected a man with some degree of heart failure, with lowered blood pressure. Against increased hypertension is the fact that the heart shadow was normal.

Could this have been pyelonephritis? It certainly could. At these sessions Dr. Mallory has pointed out to many of us how often we miss the diagnosis of chronic pyelonephritis. The diagnosis is not too easy to make. The findings in the urinary sediment when the patient comes to the hospital may be minimal, and the blood pressure elevated or normal; all forms of kidney-function tests, of course, are markedly abnormal.

Could this have been an acute renal failure due to lower-nephron defect? We have no history of the patient's having received sulfonamides or incompatible transfusion. I shall assume that they were not given, and the possibility can be discarded.

I should like to conclude with a diagnosis of carcinoma of the pylorus, diarrhea secondary to the carcinoma, chronic pyelonephritis, terminal uremia, rheumatoid arthritis, bronchiectasis and terminal heart failure.

DR. F. DENNETTE ADAMS: I am worried about Dr. Jacobson's statement that he attributed the lower border of the liver and low diaphragm to emphysema. I doubt if it could happen. I do not believe I have seen it due to that, but I may be wrong. It seems to me that a low diaphragm due to emphysema would not have enough pressure to push the liver down.

I would like to ask if perhaps amyloid disease would explain the terminal picture, especially in a man with arthritis for so many years.

DR. JACOBSON: I think I have seen a low liver — that is, a ptotic liver — pushed down by the diaphragm, even without pulmonary emphysema. In view of the demonstration of the soft-tissue mass by Dr. Wyman, I am more suspicious that the liver was the seat of carcinomatous metastases.

Against amyloid disease, I do not believe the rheumatoid arthritis was active enough to produce that

much amyloid disease. The Congo-red test was not conclusive, nor was there enough bronchiectasis in the history to suggest amyloid disease secondary to that.

Dr. John B. Stanbury: I was much impressed by one interesting physical finding. You could pass your hand through the ventral hernia and outline a firm, smooth liver as I have never been able to do before — just as well as Dr. Mallory could examine it at post-mortem examination.

The thing that puzzled us was why after operation the patient suddenly went into renal failure. He had borderline failure before operation. He had pyloric obstruction preceding operation. We took the risk. It did not work. He went quickly into renal failure, developed uremia, pulmonary edema and low chloride, went into pulmonary edema and heart failure and died. We gave him no sulfonamide.

Dr. Jacobson: No mass was felt in the abdomen through the hernia?

Dr. Stanbury: No, just the liver.

Clinical Diagnosis

Amyloid nephropathy, with uremia.

Dr. Jacobson's Diagnoses

Carcinoma of pylorus.
Chronic pyelonephritis.
Terminal uremia.
Rheumatoid arthritis.
Bronchiectasis.
Terminal heart failure.

Anatomical Diagnoses

Rheumatoid arthritis, chronic.
Amyloidosis of liver, spleen, kidneys and adrenal glands.
Bronchiectasis.
Bronchopneumonia.
Hypertrophy of heart.
Pericarditis, acute fibrinous, probably uremic.
Operative wound: resection of pylorus for obstruction.

Pathological Discussion

Dr. Mallory: Autopsy showed that several of the organs were larger than the x-ray examinations indicated. The heart weighed over 500 gm., and the liver 3500 gm. — double the normal size. The spleen weighed 500 gm., and both kidneys 450 gm. We found that the liver, spleen and kidneys showed very extensive amyloid disease and there was also some involvement of the adrenal glands. There was extensive bronchiectasis, a terminal bronchopneumonia and an acute pericarditis. The stomach, which had been resected, was a great disappointment to the pathologists. We could find nothing wrong with it. At the time of operation a biopsy on which a frozen section was done showed only normal, smooth muscle, and the resected specimen only questionable hypertrophy of the muscle of the pyloric ring and perfectly normal mucosa — neither tumor nor ulcer. Localized amyloid tumors of the gastrointestinal tract do occur, and in the face of extensive amyloid disease we thought we might find amyloid in the pyloric ring, but there was none whatever.

Dr. Edward B. D. Neuhauser: Why was a gastrectomy done?

Dr. Stanbury: There seemed to be no question that the patient had functional pyloric obstruction. Perhaps a surgeon can answer that.

Dr. W. R. Richardson: I am sorry that Dr. John McKittrick is not here. I assisted at the operation and shall try to explain our findings and the choice of procedure.

A gastrotomy was done, and the pylorus and pyloric antrum visualized. There was a definite organic obstruction at the pylorus, an annular thickening that was submucosal with no ulceration. It narrowed the lumen to a diameter of less than 1 cm. and did not permit the passage of more than the distal portion of a hemostat. This band was broken down during the digital examination, with several linear mucosal tears resulting. Much of the band was removed submucosally and sent for frozen-section diagnosis, which revealed no evidence of a malignant lesion and was eventually noted as "hypertrophy of the pylorus."

Subtotal gastrectomy was performed because it was considered inadvisable to leave traumatized areas. That this was probably an unfortunate choice is now clear, and we would have felt much better had a gastroenterostomy or even a pyloroplasty been carried out, accepting whatever hazard there might have been in leaving the traumatized pylorus and pyloric antrum.

Dr. Mallory: One cause of pyloric obstruction seen from time to time in adults is ectopic pancreatic tissue in the pyloric sphincter. We looked carefully for that but were unable to find it. I think we must assume that the pyloric obstruction was functional. I have no doubt it was real.

Dr. Jacobson: Would Dr. Ropes comment on the significance of the Congo-red test?

Dr. Marian Ropes: I think we have now seen enough cases corroborated at autopsy to say that this figure may mean amyloid disease. We still do not know what the percentages mean, but half our patients with rheumatoid arthritis show levels between 50 and 65 per cent and several have shown amyloid disease at autopsy. In addition, 15 per cent have positive levels — less than 50 per cent left in the serum. It is interesting also that the Congo-red retention does not seem to correspond with the severity of the arthritis or with the duration. We

have seen it in varying degrees of severity of arthritis.

DR. MALLORY: The amyloid deposits stained beautifully with Congo red at autopsy. It was the type that should have absorbed dye, I should think.

CASE 34532

PRESENTATION OF CASE

A forty-nine-year-old photographer entered the hospital complaining of dyspnea relieved by belching.

Five months before admission he experienced an episode of nausea, weakness and pain in the left arm, which was relieved by induced vomiting. He remained in bed for three days, and at this time a chest x-ray film showed an enlarged heart. He continued his usual activities but three months later awoke one night with sudden dyspnea, relieved by sitting on the edge of the bed for a few minutes. Since that time he had noticed gradually increasing dyspnea on exertion and frequent episodes of epigastric distress following meals, often associated with dyspnea.

Ten days prior to admission he noticed swelling of the ankles, which increased subsequently. During the past few months he had lost about 15 pounds.

Physical examination revealed a well developed, quiet man in no distress. The cardiac border was percussed 11 cm. to the left of the midline. There was a questionable diastolic gallop. The liver edge was palpated four fingerbreadths below the costal margin and was slightly tender. There was ++ edema of the ankles, extending up to the sacrum.

The temperature was 99.4°F., the pulse 90, and the respirations 24. The blood pressure was 115 systolic, 90 diastolic.

Examination of the blood revealed a hemoglobin of 14 gm., and a white-cell count of 12,000, with 77 per cent neutrophils, 19 per cent lymphocytes and 4 per cent monocytes. The urine had a specific gravity of 1.026 and gave a +++ test for albumin. Microscopical examination of the sediment showed rare red cells and 5 to 8 white cells per high-power field.

On the day following admission he experienced sudden pain in the right upper chest with a little sputum. Later a friction rub was heard on the right side, and a few rales at the right back. An x-ray film disclosed an area of somewhat mottled density lying in the anterior segment of the right upper lobe with its base against the pleura. There was a moderate quantity of fluid in the right pleural space. The lung fields otherwise appeared essentially clear except for some atelectasis in the right-lower-lung field medially. The heart shadow was enlarged to the right and left with a cardiothoracic ratio of 18:31.5; it was without characteristic configuration, and the pulsations were diminished in amplitude. Plain films of the abdomen showed the tip of the liver to lie unusually low, suggesting some enlargement of the liver. There was a hazy density obscuring some of the visceral shadows and raising the question of fluid in the abdomen. An electrocardiogram showed a normal rhythm, with a rate of 100, and a PR interval of 0.14; the T waves were inverted in Lead 1 and low in Leads 2 and 3, and there was a well marked left-axis deviation and an inverted T wave in Lead AVL with a small Q wave. The chest leads showed an upright T wave in Leads V-2 and V-4 and a flat T wave in V-5.

On the day following the episode of chest pain a bilateral superficial femoral-vein ligation was performed, and dicumarol and digitoxin were started. Tenderness of the right calf was noted on the next day. The patient continued to experience some dyspnea and occasionally raised some blood-streaked sputum. He began to run a temperature of about 100°F., and the rales at the right base persisted. The prothrombin activity became as low as 24 per cent, and digitoxin was stopped because he complained of nausea. An x-ray film on the seventh day again demonstrated the area of increased density within the anterior portion of the right upper lobe. This had increased in size since the previous examination. The right leaf of the diaphragm was considerably elevated. Very little, if any, fluid was made out. The left lung was clear. The heart was again observed to be markedly enlarged.

He continued to be nauseated and occasionally raised more bloody sputum. He developed a prominent gallop rhythm with occasional extrasystoles and dropped beats. He continued to fail slowly and developed pleural pain over the left chest posteriorly, with a loud friction rub. On the tenth hospital day he had a sudden episode of dyspnea and became increasingly cyanotic, with increase in pulse rate and lowering of blood pressure. Following this he was described as in a "chronic shocky state," and died on the following day.

DIFFERENTIAL DIAGNOSIS

DR. GORDON S. MYERS: May we see the x-ray films?

DR. STANLEY M. WYMAN: Unfortunately, we were unable to find any but these two portable films of the chest. They show the area of rather homogeneous density in the right-lung field, which appears to lie against the pleura of the anterior chest wall. There is some fluid in the fissure between the middle and lower lobes and the upper and lower lobes. The right lower lobe is decreased in size, and there is some density posteriorly, suggesting possibly another infarct. However, this film is of insufficient quality to warrant a definite conclusion. The heart shadow cannot be delineated, but it is a large heart, I believe, and is prominent in the region of the left ventricle. The left lung on these films appears clear.

DR. MYERS: Do you think the density here in the lower portion of the lobe as seen posteriorly can be consistent with pulmonary infarction?

DR. WYMAN: Yes, with some pleural fluid.

DR. BENJAMIN CASTLEMAN: This last set of films was taken on the tenth day, six days before the patient died.

DR. MYERS: I would like to begin by saying what I think the diagnosis may be and then try to explain my reasoning. I believe this man most likely had coronary-artery disease and the onset of the acute illness began with myocardial infarction, although we have no proof of that. I believe also that he had congestive failure and recurrent pulmonary emboli, both prior to and probably following treatment by superficial vein ligation and dicumarol.

The chief complaint was that of dyspnea, relieved by belching. That is an unusual chief complaint, but I suppose it is a valid one. If he had congestive failure with limitation of vital capacity and gaseous distention of the abdomen, the elevation of the diaphragm may have been responsible for some additional dyspnea, since we believe that dyspnea is proportional to ventilation divided by vital capacity.

Five months before admission this man had a curious episode of nausea, weakness and pain in the left arm, relieved by induced vomiting. That in itself is a nonspecific history. One would think, first of all, that he had something going on in the gastrointestinal tract. In view of the fact that later on we find that he had lost weight, despite the fact that he was becoming edematous, one might consider the possibility of carcinoma or some other serious lesion in the gastrointestinal tract. This history does not suggest pulmonary infarction or embolus at that time. The fact that he had pain in the left arm, even without chest pain, and that he had symptoms of indigestion certainly is consistent with the occurrence of myocardial infarction. We know that myocardial infarcts sometime occur without any symptoms. He remained in bed three days at this time. He had chest x-ray films, which showed an enlarged heart. If he had a myocardial infarct at this time, it might explain the fact that the heart appeared to be large on x-ray study and that he went on to symptoms suggesting left-sided heart failure. Thus, we can justifiably suspect myocardial infarct, but we cannot make a definite diagnosis of it from the facts at hand.

I think that the diagnosis of coronary-artery disease in a man forty-nine years old who showed congestive failure but no heart murmurs is the best bet. It is very unlikely that he had one of the rarer kinds of heart disease such as those following sulfonamide therapy and virus infection. We know that he had an episode of orthopnea. He woke up short of breath and was relieved by sitting on the edge of the bed. He had clear-cut dyspnea on exertion and also epigastric distress following meals, associated with dyspnea. If he had coronary-artery disease the symptoms of indigestion were not unusual since we know various functional gastrointestinal diseases are commonly associated with coronary disease — for example, cardiospasm, which gives symptoms of indigestion apart from the heart trouble. He may have had dyspnea after meals, partly because of abdominal distention and also because the work of the heart is increased after a full meal.

Ten days prior to admission he noted swelling of the ankles, which had increased. Despite this, he had a 15-pound weight loss, and one wonders if he had some kind of cachectic disease. I do not believe we can skip over that weight loss too lightly. However, he may have been afraid to eat, simply because eating aggravated his symptoms. Later on there is no clear-cut evidence of wasting disease such as thyrotoxicosis, cancer, diabetes or the like.

The physical examination, as stated, is consistent with congestive heart failure: there was a large heart, rapid pulse, a questionable diastolic gallop and so forth. The protocol states that the blood pressure was 115 systolic, 90 diastolic. It would be helpful to know if he had had any previous hypertension, whether or not there was venous distention, and also about the loudness of the pulmonic second sound, to get some idea whether there was pulmonary hypertension associated with left-sided heart failure.

DR. CASTLEMAN: The record states that there was distention and pulsation of the neck veins for 5 cm. above the clavicle.

DR. MYERS: That is additional evidence in favor of congestive failure. It certainly fits in with the rest of the picture.

Examination of the blood showed no definite anemia, a little increase in white-cell count and no real increase in neutrophils or lymphocytes. The urinary findings are consistent with the presence of congestive failure.

On the day following admission the patient experienced sudden pain in the right upper chest, with cough productive of a little sputum, and later a friction rub and a few rales were noted. This episode and the x-ray findings seem to be consistent with the presence of pulmonary infarction, although the small amount of fluid in the right pleural space could have been due either to congestive failure or to a pulmonary infarct that happened to be on the right side. The x-ray report states that there was atelectasis in the right-lower-lung field, but I believe that is a not uncommon statement in cases of small pulmonary infarcts. There may or may not have been additional atelectasis. The heart was large, without any special configuration, perhaps prominent in the region of the left ventricle. The cardiac pulsations were diminished. I do not believe that fact to be too helpful. Diminished pulsations may be due to the presence of pericardial fluid or simply to an enlarged, failing heart. There is certainly no evidence of constrictive pericarditis in the x-ray films or in the rest of the data that we have. The plain films of the abdomen, which we do not have here, were consistent with the presence of fluid and an enlarged liver, which were probably due to congestive heart failure.

We then come to the electrocardiograms. I am glad to have been able to see the tracings myself just now because they look a little more markedly deformed than one gathers from the description in the protocol. I am struck with the fact that there is a tendency to low voltage in the QRS complexes in the limb leads, and small R waves all across the chest, with an M-shaped QRS wave in V-5. The rest of the tracing is as stated in the protocol. The electrocardiogram is certainly not diagnostic. If one takes electrocardiograms of a large number of patients with pulmonary emboli, only about 10 per cent show characteristic findings of acute cor pulmonale. Thus, we need not be surprised when the electrocardiogram does not give us the diagnosis even if the patient had, as I assume he did, pulmonary infarcts.

How about the question of myocardial infarction? Certainly this electrocardiogram per se is not diagnostic of either old or recent myocardial infarction; however, it is consistent with coronary-artery disease, as well as with other diseases, which I do not believe we need go into because there is no other evidence in favor of them. How can the electrocardiogram be so nonspecific in acute myocardial infarction? In the first place, electrocardiograms may occasionally actually revert to normal a few months after the occurrence of a myocardial infarct. The initial episode here was five months before admission. In the second place, the localization of the myocardial infarct may be such that the standard procedure for placing the electrodes in a routine electrocardiogram fails to show the infarction even though present. The electrocardiogram may thus be normal unless special efforts are made to explore the chest thoroughly or unless an esophageal lead is taken. Third, and most important, is that serial electrocardiograms very frequently help to make the diagnosis of myocardial infarction by showing specific changes in pattern where a single tracing is of no help. Apparently, only one electrocardiogram was taken in this case. We can summarize the electrocardiographic findings by saying that although they are not diagnostic they certainly do not rule out an old anterior infarction. They are, in any case, consistent with the presence of coronary-artery disease. They do not show the typical changes of acute cor pulmonale, but we cannot be surprised at this, even in the presence of multiple pulmonary infarcts.

Following the initial episode in the hospital a superficial femoral-vein ligation was done and dicumarol given. We know that superficial femoral-vein ligations are occasionally followed by repeated pulmonary emboli, which also occur after treatment with dicumarol. It is true that superficial femoral-vein ligation is rarely followed by fatal pulmonary emboli; the same reservation holds for adequate treatment with dicumarol. The statement is made that the prothrombin level went as low as 24 per cent. That is not the important point. The point is whether over the period of treatment it had regularly been kept at a low level, somewhere between 10 and 30 per cent. If the prothrombin percentage gets down to 24 and a few days later it is up to 100, obviously we have inadequate protection for the patient. I think that the remainder of the story here is consistent with pulmonary infarcts despite the therapy that was carried out. The patient developed some cardiac arrhythmia. That may have been stimulated by the pulmonary emboli added to the presence of coronary-artery disease. The last episode before death, I believe, was more likely to have been a pulmonary embolism than myocardial infarction, although the latter is possible.

In summary, then, I believe that this patient had coronary-artery disease, with congestive failure. I believe there is a good possibility, although no proof, that he had myocardial infarction. I still think that the later episodes were pulmonary infarcts despite the dicumarol therapy and venous ligation.

Dr. Wyman: It is an unusual story for a pulmonary infarct to increase in size during the course of seven days. We are given the information that it lies against the pleural surface, but that is not entirely clear-cut from this film. I think an additional possibility that one might worry about is tumor of the lungs. I cannot exclude it from this examination.

Dr. Myers: I am grateful for your suggestion. Certainly, if there was some enlarging process in the lung atypical of pulmonary infarction, a tumor might help to explain the troublesome fact of marked weight loss in a case in which otherwise there is no definite explanation for it. I suppose the tumor, if present, could have been primary in the lung or possibly metastatic from somewhere under the diaphragm. In the latter case, it might explain the gastrointestinal symptoms that the patient had.

Dr. John B. Quinby: What would be the source of the pulmonary emboli?

Dr. Myers: I suppose from the figures available one could bet, on a 75 per cent chance, from the legs and a 25 per cent chance from the heart chambers — in which case the emboli would arise from a mural thrombus.

Dr. Quinby: Even with ligation?

Dr. Myers: Yes. Only the superficial femoral-vein ligation was performed, the profunda was not included; and also there is the possibility of clots in the iliac vessels and higher up in the pelvis.

A Physician: In how many cases of myocardial infarction have you seen the electrocardiogram return to normal?

Dr. Myers: I do not know exactly how many do.

A Physician: It certainly does occur occasionally, but how many have you seen?

Dr. Myers: I cannot answer that. Dr. White[1] has some excellent illustrations in his book showing the return of electrocardiograms to normal following myocardial infarctions.

Clinical Diagnoses

Arteriosclerotic heart disease.
Coronary thrombosis, with myocardial infarction.
Phlebothrombosis of leg, with pulmonary embolism and infarction.

Dr. Myers's Diagnoses

Coronary-artery disease, congestive heart failure, probable myocardial infarction.
Multiple pulmonary infarcts.

Anatomical Diagnoses

Coronary thrombosis, with myocardial infarction.
Mural thrombi, left ventricle and both auricles.
Pulmonary infarcts, multiple, massive.
Coronary sclerosis, severe.
Cardiac hypertrophy.
Hydrothorax, bilateral.
Central congestion of liver.
Renal infarct.

Pathological Discussion

Dr. Castleman: Autopsy showed an enlarged heart, which weighed 500 gm. The coronary arteries were very severely sclerotic. The left had a pinpoint lumen throughout, and the right was also narrowed but, in addition, contained a recently organized thrombus. The anterior portion of the left ventricle was completely infarcted. The infarction involved the interventricular septum and extended through to involve the right portion of the septum, which is a relatively rare occurrence. There was a large mural thrombus over the infarct on the left side, but none on the right. A piece of this thrombus had apparently broken off and had produced an infarct to one of the kidneys, which may perhaps account for the red cells that were found in the urine. There were mural thrombi also in both auricles so that the emboli in the lungs could be accounted for by the right auricular thrombus. The lungs were the site of numerous infarcts and very large ones, much larger than we usually see. The infarct in the right upper lobe measured 7 cm. in diameter. The increase in size of the x-ray shadow between the two sets of films was due to an infarct in the right middle lobe that occurred later, and its shadow was superimposed upon that of the upper-lobe lesion. Some years ago Dr. Hampton[2] showed that increase in size and changes in shape of infarcts may be due to other infarcts occurring close by, and that was true in the case under discussion. In addition, the entire upper portion or dorsal division of the right lower lobe and almost the entire left lower lobe were infarcted. These probably occurred after ligation, since they appeared to be redder and more recent than the others. I have the impression, and it is only an impression, that in patients with heart failure that have auricular mural thrombi as a source of emboli, the infarcts are larger than those observed when the emboli arise from the leg veins. This certainly could be borne out in this case.

The liver was enlarged and showed a severe degree of central congestion. It is surprising that he did not develop jaundice with that degree of pulmonary infarction in addition to fairly severe liver disease.

There was about 200 to 300 cc. of straw-colored fluid in the right pleural cavity, and a similar amount on the left. I think it is surprising that one cannot see anything in the left lower lobe that suggests infarct. It measured 16 by 20 cm. at autopsy. Of course, it might well have occurred during the six days between death and the time this film was taken.

Dr. Myers: How old was the myocardial infarct?

Dr. Castleman: There were several areas of recent frank necrosis and also areas of granulation tissue. I believe that some foci of infarction could have been two months old.

Dr. Myers: Were the leg veins examined?

Dr. Castleman: Yes. At the time of operation no thrombi were found in the superficial femoral veins, and at autopsy the sites of the ligation were perfectly negative. Both profundas were examined and found free from thrombus. We did find a thrombus in the popliteal vein on the right, which I think occurred following ligation.

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An index of the diagnoses and discussers of the Case Records for the year 1948 will be found elsewhere in this issue of the *Journal*.

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This issue has been prepared in two sections.

A NEW YEAR

Humility, best defined by Webster as "freedom from pride and arrogance," may be of various types and may constitute the mask that hides a variety of underlying patterns. Among these types are the self-debasing humility of the uncompensated inferiority complex; the sinister pseudohumility that characterizes the Uriah Heeps; the arrogant humility of conscious rectitude as expressed in Burton's *Anatomy of Melancholy* — "They are proud in humility; proud in that they are not proud."

There is also the honest humility of true magnanimity, fearless because it makes no pretence, recognizing superior assets and capacities in others, acknowledging powers higher than those that humankind possesses, and admitting the likelihood that even the most capable person may sometimes be in error. It is a humility of the intellect, free from pride and arrogance.

One of the errors to which any person of ambition may be liable — and the higher his road is built the deeper are the ditches that flank it — is the development of a belief in his own infallibility. Too often a genuine call to service turns with the passage of time and under the influence of personal prestige into a sense of superiority over those served. Too frequently a long period of unchallenged leadership may betray the leader into a belief in the permanence of his own position; even in his inability to make the wrong judgment. Obsessed with this feeling of unassailable righteousness, he unconsciously assumes the mantle of perfection and with it something in the way of self-bestowed divinity. In his estimation of himself he has caught up with God.

Especially vulnerable to this particular loss of perspective are those who have been drawn into fields of activity in which personal influence is a strong factor. Among these are politicians with their constituents, writers with their readers, teachers with their pupils, pastors with their parishioners, physicians with their patients. A penalty attached to their sometime loss of humility, as expressed by an eminent preacher, is that they doubt God when it is themselves that they should doubt.

To them might be recalled the words of Cromwell to Parliament, the members of which he beseeched at one time to bear in mind that they "might be mistaken."

So for everyone a resolution with which to start a new year might be to bear in mind that he may be mistaken, that true humility is a virtue that can be cultivated, and that conscious and outspoken humility is its own contradiction.

MILESTONES

Releases from public-relations counsel at times seem like those from the butcher, replete with the lard of "significance" but shy of the lean of meaning. The copywriter's incomplete comparative is familiar: the better refrigerator, the better homes

and gardens, the better postwar automobiles. Better than what? Attention is now invited by a Detroit committee of the automobile industry to a "significant" milestone, the production of a hundred million motor vehicles. A significant milestone, it may be asked, on what road?

Since the first car, fifty-five years ago, production has been at an annual rate of nearly 2,000,000 vehicles until today more than 40,000,000 cars, trucks and busses crowd the nation's highways, one for every four persons in the United States. Every minute of each working day sees 30 new cars and 10 new trucks and busses. The second hundred millionth milestone should be reached in only twenty-five more years. This informative committee avers that research and mass production have cut costs and increased sales, and in turn have increased employment, raised the nation's standard of living and expanded retail trade areas; indeed, whole new industries dependent upon this new flexible transportation tool have been developed. Since the horseless-carriage tinkerers have come out of their alleys and quit selling bicycles, the labor, the ingenuity and the lives of millions of Americans have been absorbed in the making, selling and servicing of automobiles. Many thousands of other lives, it may be stated without exaggeration, have needlessly been sacrificed as a result of their labors.

Comment has been made on accidents as a leading cause of death.[1, 2] The all-time prewar record for deaths from automobile accidents was nearly 40,000 in 1941. Although in actual numbers heart disease and cancer are the primary killers, Dickinson and Welker[3] question the adequacy of numbers of deaths as the sole measure of the relative importance of the various causes. Two new measurements are suggested: "life years lost" and "working years lost." When the latter was applied to the seven leading causes of death in four five-year periods, 1930 to 1945, accident, as a destroyer of working years, was third in 1930, second in 1935 and first in 1940. In 1945, during gas rationing, the working years lost from accidental death numbered 1,750,000, whereas those from heart disease were 1,680,000. The young white man, representing the productive strength of the country, was the special victim. It is not implied that all, but only that too many, accidental deaths are due to the automobile. One hundred million cars, trucks and busses, and 40 more per minute! This significant milestone in the production line is also a marker on the broad way that leads to destruction.

Free enterprise and fierce competition within the industry, the committee believes, is responsible for this triumph of mass production. It is suggested, on the other hand, that the achievement marks a point on the errant road of reason. Since that fall day in 1793 when a popular actress was crowned goddess of reason in Notre Dame—and in spite of the bad consciences of Robespierre and others—the modern world has believed in and depended upon reason alone. In those early days revolutionary reason was most concerned with ends. The ends were utopian: truth, justice and enlightened self-interest would bring automatic harmony between individuals and society in nature. As absolutism and authoritarianism were crushed, new creative activity was released, bringing rapid advances in politics, economics, education and technics. With apparently complete success of republicanism and industrialism in the nineteenth century, revolutionary reason or the reason of ends was sacrificed to technical reason or the reason of means. This technical reason has produced the present large-scale, industrial, competitive, mass-producing economy rising above physical nature and man himself and its heretical counterpart the totalitarian state with its "planning reason."[4] The hundred millionth motor vehicle is the crown of technical knowledge.

This apogee of the assembly line, it is agreed, is a milestone of some sort. Yet 40,000 deaths a year is only a pace on the way of man against himself, since the atom bomb can do twice or three times as well in the twinkling of an eye. This record production of automobiles is a signal achievement on the road of technical reason, but this road remains the blind alley of men's hope. Nevertheless, whatever road it is, the automobile industry should be joined in their self-congratulation on their milestone. Let the public-relations counsel tot up the blessings of industrial culture at this season! One looks hopefully for a release from someone about a milestone,

however insignificant, on the straight and narrow path that leads to peace and good will among men.

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HANDKERCHIEFS AND THE TRANSFER OF RESPIRATORY INFECTIONS

"Don't put a cold in your pocket" is a slogan used by manufacturers of disposable tissues and designed to sell the public on the idea of substituting their product for the traditional handkerchief. The use of the latter, however, has long been thought to be an effective means of protecting others from infections. A sneeze or cough not protected by a handkerchief has been considered by many as tantamount to a direct assault on the health of one's neighbors — a sort of peacetime version of bacterial warfare. Some recent considerations of the possible role of the handkerchief in the spread of respiratory infections may provide further ammunition for the sales talks against the handkerchief although they offer little solace when it comes to the virtues of the tissues.

In one of the latest studies to be reported in this connection,[1] an estimate was made of the number of bacteria-carrying particles that can be shaken into the air from the handkerchiefs of people with and without nasal discharge. The average number of such particles in a series of 211 handkerchiefs was about 130,000. The particles were large enough to suggest that they each carried a number of bacteria. The predominant organism recovered was *Staphylococcus aureus* and corresponded with those found in cultures of nasal swabs or of the skin of the same subjects. In some cases nonhemolytic streptococci similar to those of the throat and mouth flora were found.

This study was carried out at the Harvard Hospital in England, where investigations are being conducted on the transmission of the common cold. Interestingly enough, there was but small difference between the average counts of infected particles shaken from the handkerchiefs of persons without nasal discharge and the counts of those with nasal discharge that was either slight, profuse or even purulent.

Because of the recent great interest in aerial disinfectants, studies were made of the effects of some of these agents on the bacteria shed from the handkerchiefs into the air. The infectious particles were found to be resistant to the action of several of the more potent of these aerial disinfectants, including ultraviolet rays and triethylene glycol, employed in the usual concentrations and at normal relative humidities.

Hamburger and Green[2] had previously called attention to the problem of the dangerous carriers of hemolytic streptococci when they found that large numbers of these bacteria could be recovered from the hands of nasal carriers. Hamburger[3] subsequently reported that literally hundreds of thousands of virulent hemolytic streptococci could frequently be recovered from the hands of such carriers. Furthermore, several hundred to almost 50,000 of these pathogens could be transferred to the hands of a noncarrier by an ordinary handshake. The greatest numbers were transferred by carriers who had just blown their noses into sterile handkerchiefs.

Although these experiments were not repeated with materials other than handkerchiefs, it is quite certain that the results would not have been very different had the subjects blown their noses into the best advertised of tissues and discarded them instead of using sterile handkerchiefs, which they would then have put into their pockets.

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INFANT INVESTIGATOR

It is hard to realize that Dr. Arnold Gesell, after thirty-seven years on the Yale faculty, during most of which time he has been director of Yale's famous Clinic of Child Development, has retired — in order to expand his works still further. Some of Dr. Gesell's books, of which there are a full two dozen,

have been the vade mecum of the intellectual young mother, determined that she will rear only superior children. All of them, reporting on territory explored largely by their author, have been enlightening texts on infant behavior and books of reference for the pediatrician and the psychologist.

If one lesson only that Dr. Gesell taught were to be selected as his greatest contribution, it would be that each infant is a person, with its own appetites and satisfactions, its own capacities and its own built-in timing mechanism.

Dr. Gesell, now that he has demonstrated to the world all there is at present to know about child behavior (from the age of four months on), will continue his investigations at Yale University in charge of a child vision research project, under a grant from the American Optical Company. Those who have taken to heart the injunction that where there is no vision the people perish will rejoice that this work is to be under such able direction. Dr. Gesell's pupils, disciples and other fans will wish him continued success in his new work. They may perhaps, looking a long way back, be reminded of another investigator in better vision to whom has been given the credit for the invention of spectacles — Roger Bacon, the Dr. Mirabilis of his day.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CHANGES IN ISOLATION AND QUARANTINE REQUIREMENTS

The Department has recently made a number of changes in the list of reportable diseases and in the isolation and quarantine requirements. These changes will go into effect as soon as a printing of the revised regulations can be obtained and distribution made to boards of health, school departments, hospitals and other agencies.

To inform physicians of these changes, the following brief résumé is included in this column.

Infectious hepatitis has been added to the list of reportable diseases; hookworm disease, lobar pneumonia and suppurative conjunctivitis have been removed from the list.

Hereafter, there will be no differentiation in the handling of immune and nonimmune contacts of communicable diseases.

Poliomyelitis. The term "poliomyelitis" will be used instead of the former designation, "anterior poliomyelitis." This will change the order of the disease in the list and in the table of isolation and quarantine requirements. The deletion of the phrase "and thereafter until acute symptoms have subsided" leaves the isolation of the patient as a period of two weeks from the onset of the disease. All restrictions upon contacts, whether adults or children, have been removed. A placard will no longer be required for the disease.

Chancroid. There will be no restrictions upon contacts of this disease.

Chicken pox. The period of isolation will be seven days from the appearance of the eruption.

Diphtheria. The minimum time limit of one week for isolation of the patient has been eliminated. The patient will be isolated until clinical recovery and the obtaining of negative cultures. There will be no restrictions upon adult contacts of diphtheria, but child contacts will be excluded from school for one week after the patient has been hospitalized or until the child has lived away from home for one week.

Granuloma inguinale. There will be no restrictions upon contacts of patients with this disease.

Infectious hepatitis. Patients will be isolated for the duration of fever. There will be no restrictions upon contacts.

Leprosy. There will be no isolation of patients with leprosy.

Lymphogranuloma venereum. There will be no restrictions upon contacts of patients with this disease.

Meningitis, meningococcal. Patients will be isolated for only three days from the beginning of adequate sulfonamide therapy. There will be no restrictions upon contacts.

Meningitis, other forms. No isolation will be imposed upon cases of meningitis due to organisms other than the meningococcus.

Mumps. The patient with mumps will be isolated for a week from the onset of the disease, the reference to swelling of the salivary glands being eliminated from the regulations.

Ophthalmia neonatorum. Infants with infected eyes will be isolated only until two negative smears or cultures to rule out gonococcal ophthalmia have been obtained.

Salmonellosis. All paratyphoid infections will be included under this designation.

Plague. The new regulations place restrictions upon contacts of patients with plague only in pneumonic cases, in which the contacts are quarantined for seven days after the last exposure.

Scarlet fever. Isolation of both adults and children has been reduced to one week from appearance of the rash, and thereafter until clinically recovered, and until purulent discharges, if any, have ceased. Children may be allowed to go to school within one week after patient has been under adequate treatment, or the patient has been hospitalized.

Whooping cough. There will be no restrictions upon contacts of patients with whooping cough.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The January schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Clinic	Date	Clinic Consultant
Salem	January 3	Paul W. Hugenberger
Haverhill	January 5	William T. Green
Lowell	January 7	Albert H. Brewster
Greenfield	January 10	Charles L. Sturdevant
Gardner	January 11	Carter R. Rowe
Brockton	January 13	George W. Van Gorder
Springfield	January 18	Garry deN. Hough, Jr.
Pittsfield	January 19	Frank A. Slowick
Hyannis	January 20	Paul L. Norton
Worcester	January 21	John W. O'Meara
Fall River	January 24	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

A CORRECTION

To the Editor: In an excellent review of the book *Hodgkin's Disease and Allied Diseases* by Parker and Jackson in the December 2 issue of the *Journal* there are two factual errors. The review is clearly written by a man of experience and knowledge so that these errors may easily have slipped into the preparation of the manuscript. Nevertheless, I believe that they should be corrected. In the review it is stated that we suggest dropping the term endothelioma, which was not intended. We *do* require a complete autopsy before such a diagnosis is made, for endothelioma, frequent in Java, may very closely simulate undifferentiated carcinoma and unless this condition can be ruled out we believe a diagnosis of endothelioma is unwise. Secondly, the reviewer, though twice using the term giant-follicle lymphoma, once refers to giant-follicle lymphosarcoma. In our opinion "giant-follicle lymphosarcoma" does not and, indeed, cannot exist, even though practically all students of the subject agree that giant-follicle lymphoma frequently progresses, with the passage of time, into lymphosarcoma. The diagnosis, treatment and prognosis is then that of the latter condition — lymphosarcoma.

Henry Jackson, Jr., M.D.

Mallory Institute of Pathology
Boston City Hospital

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

History of the Medical Society of the District of Columbia. Part II, 1833-1944. History Committee: John Benjamin Nichols, chairman, William Johnston Mallory and Joseph Stiles Wall. 8°, cloth, 357 pp., with 13 illustrations and frontispiece. Baltimore: Waverley Press, Incorporated, 1947.

This second volume of the history of the Society continues the narrative to approximately July 1, 1944. All the activities of the Society are covered, and a list of members from 1833 to 1911 is appended to the text. Two indexes with subjects and personal names conclude the volume. The book is well published and is recommended for history of medicine collections.

Gardiner's Handbook of Skin Diseases. Revised by John Kinnear, O.B.E., T.D., M.D., M.R.C.P. (Ed.), D.L., lecturer in diseases of the skin, St. Andrews University, physician for diseases of the skin, Dundee Royal Infirmary, and dermatologist, pre-school and school medical services, Dundee. Fifth edition. 12°, cloth, 250 pp., with 80 illustrations and colored plates. Baltimore: The Williams and Wilkins Company, 1948. $4.50.

This fifth edition of a popular manual, first printed in 1919, has been revised to bring it up to date since the printing of the third edition in 1939. The text was printed in Great Britain and bound in the United States. The volume reflects the British aspect of dermatology.

The Year Book of Pathology and Clinical Pathology. "Pathology," editor, Howard T. Karsner, M.D., professor of pathology, director of the Institute of Pathology, Western Reserve University, Cleveland; assistant editor, Herbert Z. Lund, M.D., assistant professor of pathology, Western Reserve University, Cleveland. "Clinical Pathology," editor, Arthur H. Sanford, M.D., professor of clinical pathology, University of Minnesota (The Mayo Foundation), and senior consultant, Division of Clinical Laboratories, Mayo Clinic. 12°, cloth, 558 pp., with 102 illustrations. Chicago: The Year Book Publishers, Incorporated, 1948. $3.75.

The Year Book of Pathology ceased publication in 1941 because of war and post-war conditions. It has now been reissued, and the present volume abstracts the literature for the year 1947. The volume is well published and is recommended for all medical libraries and to persons interested in the subject.

Ophthalmology in the War Years. Edited by Meyer Wiener, M.D., professor of clinical ophthalmology, Washington University School of Medicine, and honorary consultant in ophthalmology, Bureau of Medicine and Surgery, United States Navy. Volume II (1944-June, 1946). 8°, cloth, 997 pp. Chicago: The Year Book Publishers, Incorporated, 1948. $16.00.

This second volume attempts to include in the reviews everything of importance published during the period of two and a half years from 1944 to June, 1946. Thirty-seven persons have contributed to the volume. A few chapters not in the first volume have been added to make the work complete and up to date. Articles not discussed in the reviews have been listed in the bibliographies appended to the chapters. Comprehensive indexes of subjects and authors conclude the volume. The type and paper are good, and the printing excellent. The work is recommended for all medical libraries and ophthalmologists.

Essentials of Fevers. By Gerald E. Breen, M.D., B.Ch. (N.U.I. Dub.), D.P.H., D.O.M.S. (R.C.P. Lond., R.C.S. Eng.). Second edition. 16°, cloth, 351 pp., with 23 illustrations and 17 plates. Baltimore: The Williams and Wilkins Company, 1948. $4.50.

This second edition of a manual, first published in 1939, has been revised to include new sections on typhus, glandular and undulant fevers, influenza and encephalitis lethargica. Additions have been made to the chapters on sore throat and food poisoning. The article on dysentery has been rewritten and expanded. Color plates have been included for the first time. The type, printing and paper are good (the book was printed in Great Britain). The manual should prove useful as a reference source for the general practitioner.

Conference on Metabolic Aspects of Convalescence. Transactions of the fifteenth meeting. Edited by Edward C. Reifenstein, Jr., M.D. 8°, paper, 163 pp., with 35 illustrations. New York: Josiah Macy, Jr. Foundation, 1947. $2.25.

This conference was featured by a symposium on the isotopes with fourteen persons participating. Eighteen other persons contributed discussions on various aspects of metabolism. The different conferences of the Macy Foundation should be in all medical libraries.

NOTICES

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

30 Bennet Street, Boston
Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

Tuesday, January 4 — Vitamin B_{12} Therapy in Pernicious Anemia. Dr. Abraham Frumin.

Friday, January 7 — Carcinoma of the Cervix. Dr. Howard Ulfelder.

Wednesday, January 12 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, January 14 — Differential Spinal Block. Dr. Stanley J. Sarnoff.

Tuesday, January 18 — *Journal* review.

Friday, January 21 — Simplified Blood Sugar Screening Method. Dr. Hugh L. C. Wilkerson.

Tuesday, January 25 — The Clinical Use of Washed Red Cell Transfusions. Dr. Jacob Neber.

Friday, January 28 — The Use of Tests that Measure Hepatic Excretory Functions. Dr. Albert I. Mendeloff.

On Tuesday morning, January 11, from 9 to 10 o'clock and on Wednesday mornings, January 5, 19 and 26, from 9 to 10 o'clock, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Thursday mornings from 9 to 10 o'clock clinics will be given by Dr. William Dameshek.

On the second and fourth Fridays of the month, January 14 and 28, therapeutic conferences will be held with round-table discussion from 2 to 4 o'clock (Dr. Robert P. McCombs, moderator). On the second and fourth Fridays, January 14 and 28, Dr. Merrill Sosman will conduct x-ray conferences from 4 to 6 o'clock. On Saturday mornings from 9 to 10 o'clock surgical clinics will be given by Dr. C. Stuart Welch. Medical rounds are conducted each weekday except Saturday by members of the hospital staff from 12 to 1 o'clock.

All exercises are open to the medical profession.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, January 6, at 7:15 p.m. in the classroom of the Nurses' Residence. Dr. Cleaveland Floyd will speak on the subject "Miliary Tuberculosis." Dr. Pauline Luzackas will be chairman.

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the amphitheater of the Dowling Building, Boston City Hospital, on Monday, January 10, at 8:15 p.m., Dr. Laurence B. Ellis presiding.

PROGRAM

Functional Renal Insufficiency Precipitated in Patients with Congestive Failure by Sodium Depletion. Drs. Frank Drinan and Kermit H. Katz.

Mitral Stenosis, with Special Reference to Surgical Intervention.

Clinical-Physiologic Correlations. Drs. Laurence B. Ellis, J. G. Mebane, George Maresh, W. K. Long, and R. A. Bloomfield.

Experimental Studies on Mitral-Valve Function. Dr. Leona R. Norman.

Surgical Aspects. Dr. Dwight E. Harken.

Thrombosis in Arteriosclerosis of the Lower Extremities. Dr. Edward A. Edwards.

Interested physicians and medical students are cordially invited to attend.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, January 11, at 8:00 p.m. The scientific program will consist of the following:

Changes in Body Fluid Chemistry as They Affect Preoperative and Postoperative Care. Francis D. Moore, M.D.

The Clinical Aspects of Pulmonary Atelectasis. Cutting B. Favour, M.D.

Pathologic Aspects of Postoperative Pulmonary Atelectasis. Joseph D. Boggs, M.D.

Aspiration Bronchoscopy in the Treatment of Postoperative Pulmonary Atelectasis. William S. Derrick, M.D.

Physicians and medical students are invited.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, January 11 at 8:00 p.m. The chairman for the evening is Dr. Raymond D. Adams.

PROGRAM

The Correlation between Morphologic and Functional Disorders in the Motor-Nerve Cells in Poliomyelitis. Derek E. Denny-Brown and Joseph M. Foley.

An Encephalomyelitic Virus of Mice Causing Demyelinating Lesions of the Central Nervous System. F. Sargent Cheever, O. T. Bailey and A. M. Pappenheimer.

Pathological Changes in Carbon Monoxide Poisoning. Charles S. Kubik.

Subsequent meetings will be held on February 8, March 8, April 12 and May 10.

SUFFOLK DISTRICT MEDICAL SOCIETY

The third medicolegal meeting of the Suffolk District Medical Society and the Boston Bar Association will be held in Ware Hall, Boston Medical Library, on Wednesday, January 12, at 8 p.m. Dr. Alan R. Moritz will speak on the subject "Scientific and Medical Tests in Legal Proceedings," which will be discussed by Mr. Arthur F. Bickford, prominent Boston trial lawyer.

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, January 26.

After the business meeting of the evening, Dr. Bronson Crothers will speak on the subject, "The Position of the Pediatrician in Relation to Specialists of Various Categories, Present and Impending."

Further details concerning the meeting will be forthcoming at a later date.

UNIVERSITY OF WISCONSIN SYMPOSIUM ON SCIENCE AND CIVILIZATION

As part of the general celebration of the centennial anniversary of the University of Wisconsin, the University's History of Science Group is sponsoring a symposium on "Science and Civilization." This symposium will be held January 13-15 at the Memorial Union of the University of Wisconsin in Madison.

MISSISSIPPI VALLEY MEDICAL SOCIETY

The annual meeting of the Mississippi Valley Medical Society will be held at the Jefferson Hotel, St. Louis, Missouri, from September 28 to 30, under the presidency of Dr. Alphonse McMahon, of St. Louis University.

(*Notices concluded on page vii*)

NOTICES (*Concluded from page 1060*)

AMERICAN MEDICAL ASSOCIATION COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

The forty-ninth annual congress on medical education and licensure will be held in the Red Lacquer Room, Palmer House, Chicago, on February 7 and 8. The fourth annual conference on rural health (sponsored by the Committee on Rural Health of the American Medical Association), will be held in the Red Lacquer Room, Palmer House, Chicago on February 4 and 5 from 9:30 a.m. to 5:00 p.m. On February 5 the Advisory Board for Medical Specialties will hold an open meeting in the Crystal Room, Palmer House, Chicago (time to be announced later). From 9:30 a.m. to 5:00 p.m. the National Conference on Medical Service, sponsored by officers of state medical societies, will be held in the Red Lacquer Room, Palmer House, Chicago.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1949 ESSAY CONTEST

The Ninth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1949. The society will offer a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Fourteenth Annual Meeting of the Mississippi Valley Medical Society to be held in St. Louis, Missouri, September 28, 29 and 30, 1949, the society reserving the exclusive right to first publish the essay in its official publication — the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1949. The winning essays in the 1948 contest appear in the January 1949 issue of the *Mississippi Valley Medical Journal*. Further details may be obtained from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 6

THURSDAY, JANUARY 6

7:15 p.m. Monthly Clinical Conference and Staff Meeting. New England Hospital for Women and Children. Classroom of Nurses' Residence.

FRIDAY, JANUARY 7

*9:00–10:00 a.m. Carcinoma of the Cervix. Dr. Howard Ulfelder. Joseph H. Pratt Diagnostic Hospital.

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

MONDAY, JANUARY 10

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*8:15 p.m. New England Heart Association. Amphitheater, Dowling Building, Boston City Hospital.

TUESDAY, JANUARY 11

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*8:00 p.m. New England Society of Anesthesiologists. Auditorium of Building A, Boston University School of Medicine.

8:00 p.m. Harvard Medical Society. Amphitheater, Building D, Harvard Medical School.

WEDNESDAY, JANUARY 12

*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m.–12:00 m. Medical Rounds. Amphitheater, Children's Hospital.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

8:00 p.m. Medicolegal Meeting, Suffolk District Medical Society and the Boston Bar Association. Ware Hall, Boston Medical Library.

*Open to the medical profession.

JANUARY 4–28. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Page 1060.

JANUARY 6. New England Hospital for Women and Children. Page 1060.

JANUARY 7–APRIL 13, 1949. American College of Surgeons. Sectional Meetings. Page xi, issue of December 23.

JANUARY 10. New England Heart Association. Page 1060.

JANUARY 11. Harvard Medical Society. Page 1060.

JANUARY 11. New England Society of Anesthesiologists. Page 1060.

JANUARY 12. Suffolk District Medical Society. Page 1060.

JANUARY 13. The Present Status of the Peptic Ulcer Problem. Dr. S. Allan Wilkinson. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JANUARY 13–15. University of Wisconsin Symposium on Science and Civilization. Page 1060.

JANUARY 26. New England Pediatric Society. Page 1060.

JANUARY 27–29. American Association of Schools of Social Work. Page 984, issue of December 16.

MARCH 7–9. American Academy of General Practice. Page 728, issue of November 4.

MARCH 28–APRIL 1. American College of Physicians. Page 158, issue of July 22.

MAY 16–19. American Urological Association. Biltmore Hotel, Los Angeles, California.

MAY 24–26. Massachusetts Medical Society. Annual Meeting. Worcester Memorial Auditorium, Worcester.

MAY 26–28. American Goiter Association. Hotel Loraine, Madison, Wisconsin.

MAY 30—JUNE 3. International Congress on Rheumatic Diseases. Page 800, issue of November 18.

SEPTEMBER 28–30. Mississippi Valley Medical Society. Page 1060.

NOVEMBER 11–17. Third Inter-American Congress of Radiology. Page 158, issue of July 22.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

JANUARY 25. 8:30 p.m. Academy of Medicine, Springfield. A Review of the Sterility Problem. Dr. John Rock.

APRIL 26. 6:00 p.m. Hotel Highland, Springfield. (Dinner Meeting.) Convulsive Disorders. Dr. Douglas T. Davidson.

HAMPSHIRE

JANUARY 5. 4:30 p.m. Experiences on a Medical Mission in Europe. Dr. Alexander M. Burgess.

MARCH 2. 4:30 p.m. The Present Status of Treatment of Coronary Disease. Dr. Clarence E. de la Chapelle.

MAY 4. Annual Meeting and Election of Officers.

MIDDLESEX EAST

JANUARY 19.

MARCH 23.

MAY 11.

SUFFOLK

JANUARY 12. Joint Medicolegal Meeting with Boston Bar Association. Ware Hall, Boston Medical Library. Scientific and Medical Tests in Legal Proceedings. Dr. Alan R. Moritz.

WORCESTER NORTH

FEBRUARY 23. Burbank Hospital, Fitchburg.

APRIL 27. Annual Meeting.

TWO-WAY PROTECTION

Tablets FERROSATE (Kenmore)

(Ferrous Sulfate, gr. iv)

are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages:

1 Inner coating prevents premature oxidation in vivo.

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Old Way...

CURING RICKETS in the CLEFT of an ASH TREE

FOR many centuries,—and apparently down to the present time, even in this country—ricketic children have been passed through a cleft ash tree to cure them of their rickets, and thenceforth a sympathetic relationship was supposed to exist between them and the tree.

Frazer* states that the ordinary mode of effecting the cure is to split a young ash sapling longitudinally for a few feet and pass the child, naked, either three times or three times three through the fissure at sunrise. In the West of England, it is said the passage must be "against the sun." As soon as the ceremony is performed, the tree is bound tightly up and the fissure plastered over with mud or clay. The belief is that just as the cleft in the tree will be healed, so the child's body will be healed, but that if the rift in the tree remains open, the deformity in the child will remain, too, and if the tree were to die, the death of the child would surely follow.

*Frazer, J. G.: The Golden Bough, vol. 1, New York, Macmillan & Co., 1922

It is ironical that the practice of attempting to cure rickets by holding the child in the cleft of an ash tree was associated with the rising of the sun, the light of which we now know is in itself one of Nature's specifics.

New Way...

Preventing and Curing Rickets *with* OLEUM PERCOMORPHUM

NOWADAYS, the physician has at his command, Mead's Oleum Percomorphum, a Council-Accepted vitamin D product which actually prevents and cures rickets, when given in proper dosage.

Like other specifics for other diseases, larger dosage may be required for extreme cases. It is safe to say that when used in the indicated dosage, Mead's Oleum Percomorphum is a specific in almost all cases of rickets, regardless of degree and duration. Mead's Oleum Percomorphum because of its high vitamins A and D content is also useful in deficiency conditions such as tetany, osteomalacia and xerophthalmia.

* * *

COUNCIL-ACCEPTED

Oleum Percomorphum With Other Fish-Liver Oils and Viosterol. Contains 60,000 vitamin A units and 8,500 vitamin D units per gram and is supplied in 10 c.c. and 50 c.c. bottles; and in bottles containing 50 and 250 capsules.

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